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1997

Atlas of Tumor Pathology

Tumors of the Mediastinum

by
Yukio Shimosato, M.D.
and
Kiyoshi Mukai, M.D.

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Atlas of Tumor Pathology

ATLAS OF TUMOR PATHOLOGY

Third Series
Fascicle 21

TUMORS OF THE MEDIASTINUM

by

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Published by the
ARMED FORCES INSTITUTE OF PATHOLOGY
Washington, D.C.

Under the Auspices of
UNIVERSITIES ASSOCIATED FOR RESEARCH AND EDUCATION IN PATHOLOGY, INC.
Bethesda, Maryland
1997

Accepted for Publication
1995

Available from the American Registry of Pathology
Armed Forces Institute of Pathology
Washington, D.C. 20306-6000
ISSN 0160-6344
ISBN 1-881041-30-1

RD
651
A862
Fasc. 21
1987

ATLAS OF TUMOR PATHOLOGY

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EDITORS' NOTE

The Atlas of Tumor Pathology has a long and distinguished history. It was first conceived at a Cancer Research Meeting held in St. Louis in September 1947 as an attempt to standardize the nomenclature of neoplastic diseases. The first series was sponsored by the National Academy of Sciences-National Research Council. The organization of this Sisyphean effort was entrusted to the Subcommittee on Oncology of the Committee on Pathology, and Dr. Arthur Purdy Stout was the first editor-in-chief. Many of the illustrations were provided by the Medical Illustration Service of the Armed Forces Institute of Pathology, the type was set by the Government Printing Office, and the final printing was done at the Armed Forces Institute of Pathology (hence the colloquial appellation "AFIP Fascicles"). The American Registry of Pathology purchased the Fascicles from the Government Printing Office and sold them virtually at cost. Over a period of 20 years, approximately 15,000 copies each of nearly 40 Fascicles were produced. The worldwide impact that these publications have had over the years has largely surpassed the original goal. They quickly became among the most influential publications on tumor pathology ever written, primarily because of their overall high quality but also because their low cost made them easily accessible to pathologists and other students of oncology the world over.

Upon completion of the first series, the National Academy of Sciences-National Research Council handed further pursuit of the project over to the newly created Universities Associated for Research and Education in Pathology (UAREP). A second series was started, generously supported by grants from the AFIP, the National Cancer Institute, and the American Cancer Society. Dr. Harlan I. Firminger became the editor-in-chief and was succeeded by Dr. William H. Hartmann. The second series Fascicles were produced as bound volumes instead of loose leaflets. They featured a more comprehensive coverage of the subjects, to the extent that the Fascicles could no longer be regarded as "atlases" but rather as monographs describing and illustrating in detail the tumors and tumor-like conditions of the various organs and systems.

Once the second series was completed, with a success that matched that of the first, UAREP and AFIP decided to embark on a third series. A new editor-in-chief and an associate editor were selected, and a distinguished editorial board was appointed. The mandate for the third series remains the same as for the previous ones, i.e., to oversee the production of an eminently practical publication with surgical pathologists as its primary audience, but also aimed at other workers in oncology. The main purposes of this series are to promote a consistent, unified, and biologically sound nomenclature; to guide the surgical pathologist in the diagnosis of the various tumors and tumor-like lesions; and to provide relevant histogenetic, pathogenetic, and clinicopathologic information on these entities. Just as the second series included data obtained from ultrastructural (and, in the more recent Fascicles, immunohistochemical) examination, the third series will, in addition, incorporate pertinent information obtained with the newer molecular biology techniques. As in the past, a continuous attempt will be made to correlate, whenever possible, the nomenclature used in the Fascicles with that proposed by the World Health Organization's International Histological Classification of Tumors. The format of the third series has been changed in order to incorporate additional items and to ensure a consistency of style throughout. Close cooperation between the various authors and their respective liaisons from the editorial board will be emphasized to minimize unnecessary repetition and discrepancies in the text and illustrations.

To its everlasting credit, the participation and commitment of the AFIP to this venture is even more substantial and encompassing than in previous series. It now extends to virtually all scientific, technical, and financial aspects of the production.

The task confronting the organizations and individuals involved in the third series is even more daunting than in the preceding efforts because of the ever-increasing complexity of the matter at hand. It is hoped that this combined effort—of which, needless to say, that represented by the authors is first and foremost—will result in a series worthy of its two illustrious predecessors and will be a suitable introduction to the tumor pathology of the twenty-first century.

Juan Rosai, M.D.
Leslie H. Sobin, M.D.

PREFACE AND ACKNOWLEDGMENTS

Twenty years have passed since the publication of the Second Series of this Fascicle, and during this period additional knowledge has accumulated, particularly on the pathobiology of thymic epithelial tumors, both thymoma and thymic carcinoma, lymphoid tumors, and germ cell tumors. At the time of that publication, the general belief had been that the grade of malignancy of thymoma could not be determined by histologic examination alone, although a spindle cell variety was known to have a better prognosis, and that invasiveness was considered the most important factor in determining the outcome of the disease. However, for the last 10 years or so, nuclear and nucleolar morphology, mitotic activity, and epithelial predominance with certain histologic features by themselves have been found to be reliable indices of aggressive behavior and to be of prognostic importance, and a new "histogenetic" classification was proposed by Professor H. K. Müller-Hermelink and coworkers. Pathologists now recognize such relatively aggressive tumors among thymomas, but no standard histologic subtyping of thymic epithelial tumors has yet been devised. Many publications on tumors of organs other than the thymus use the classification of either the World Health Organization (WHO) or some other internationally authorized committee. In the absence of a standard classification system for thymic tumors, we modified the histologic classification scheme for thymic epithelial tumors developed years ago by the Mayo Clinic Group and used worldwide for many years, by incorporating the classification of Rosai and Levine in the Second Series of this Fascicle and that proposed by Müller-Hermelink et al., the latter of which has been accepted by pathologists and clinicians in some European countries and at some hospitals in the United States and Asia as clinically more applicable than the conventional classification scheme. Currently, search continues for appropriate terminology in order to unify these classifications into a standard, since there is agreement on the possible outcome of given tumors with certain histology. The classification system described in this Fascicle is compatible with both classifications and is interconvertible with each. We owe much to Drs. Juan Rosai, Nancy Lee Harris, and Cesar Moran of the United States, Drs. H. K. Müller-Hermelink and T. Kirchner of Germany, Dr. Kristine Henry of the United Kingdom, and Dr. Tseng-tong Kuo of Taiwan.

Concerning thymic carcinomas, i.e., malignant thymoma, category 2 according to Rosai and Levine, a fairly large number of cases have accumulated, making it possible to subclassify them and correlate pathology with clinical course. Promising therapeutic results are being obtained for malignant germ cell tumors, with the expectation of an increase in the cure rate in the near future. We have described new entities and altered our understanding of the nature of some tumors reported.

Most of the cases used in this Fascicle are from the pathology files at the National Cancer Center Hospital in Tokyo and the Matsudo Hospital of the National Sanatorium (which became integrated into the National Cancer Center Hospital East 4 years ago); Dr. Tetsuro Kodama, the person responsible for filing the pathology materials, kindly supplied us with the pathology material and clinical data we needed. Other cases are from consultation material that was sent to us. Cases with which we had no personal experience and material that was not in our possession were generously supplied by many pathologists in Japan, the United States, and Europe, and included original data published in scientific journals as well as photographs used in the First and Second Series of this Fascicle. Invaluable advice came from the Editor of the Third Series, Dr. Juan Rosai, Associate Editor Dr. Leslie Sobin, and Editorial Consultant Dr. Richard Kempson, who deserve special mention for their critical review of the

manuscript, and for their patience with regard to some delay in its completion. We would also like to express our gratitude to those who made direct and important contributions to the preparation of this manuscript: Ms. Reiko Yamane who edited and typed the manuscript repeatedly and Mr. Shunji Osaka who prepared more than several hundred microphotographs with great skill. Finally we wish to express sincere thanks to our former teachers in surgical pathology, and to acknowledge the contributions of our colleagues, both chest physicians and surgeons, pathologists, pathology trainees, and research fellows at the National Cancer Center Hospital and Research Institute. Although this book has been completed with the support of many individuals, the opinions and assertions it contains are the personal views of the authors and are not to be construed as entirely reflecting the view of the Chest Group at the National Cancer Center Hospitals.

Yukio Shimosato, M.D.
Kiyoshi Mukai, M.D.

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Am J Pathol 1988;133:615–22. For figures 3-97 and 3-98.

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Am J Surg Pathol 1982;6:451–70. For figure 3-135.
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Cell Tissue Res 1984;237:227–37. For table 1-2 and figure 1-10.
Current Top Pathol 1986;75:207–68. For tables 1-1, 1-2, 1-3, and figures 1-9 and 1-10 B,C,D.

Williams & Wilkins:
Neoplastic Hematopathology, 1992. For figures 1-19, 3-194, 3-203, 4-26, and 4-27.

Contents

1. Anatomy and Anatomic Compartments of the Mediastinum 1
   Normal Thymus Gland 1
2. Non-Neoplastic Conditions of the Thymus 23
   Thymus in Immunodeficiency 23
      Thymus in Primary Immunodeficiencies 24
      Thymus in Secondary Immunodeficiencies 26
   Thymic Hyperplasia 26
      True Thymic Hyperplasia 27
      Lymphoid Hyperplasia 28
3. Tumors of the Thymus and Related Lesions 33
   Classification 33
   Thymolipoma and Hamartomatous Lesions 33
      Thymolipoma 33
      Ectopic Hamartomatous Thymoma 38
   Epithelial Tumors 40
      Thymoma 40
      Thymic Carcinoma 120
   Carcinoid and Related Tumors 158
   Germ Cell Tumors 183
   Malignant Lymphoma 207
      Hodgkin's Disease 207
      Lymphoblastic Lymphoma 212
      Large Cell Lymphoma 214
      Atypical Hyperplastic Lymphoepithelial Lesion and Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma 221
   Secondary Involvement of the Thymus by Carcinoma and Mesothelioma (Including Solitary Fibrous Tumor) 227
      Secondary Carcinoma Involving the Thymus 227
      Distinction Between Thymic and Pulmonary Carcinomas 228
      Mesothelioma Involving the Thymus and Solitary Fibrous Tumor 229
   Tumor-Like Lesions of the Thymus 233
      Thymic Cyst 233
      Other Tumor-Like Lesions 236
   Ectopic Tissues and Tumors in the Anterosuperior Mediastinum 237
      Thyroid Lesions 237
      Parathyroid Lesions 238
4. Tumors of the Mediastinum Excluding the Thymus, Heart, and Great Vessels 249
   Mesenchymal Tumors 249
      Benign Mesenchymal Tumors and Tumor-Like Lesions 249
      Malignant Mesenchymal Tumors 253
   Neurogenic Tumors and Tumors of Paraganglia 256
      Immunohistochemistry of Neurogenic Tumors and Paragangliomas 263

Mediastinal Cysts (Other than Thymic Cyst) 263
Bronchogenic Cyst 264
Esophageal Cyst 265
Gastroenteric Cyst 265
Celomic Cyst (Pericardial Cyst and Mesothelial Cyst) 266
Thoracic Duct Cyst 266
Cyst-Like Lesions Other Than True Cysts 266
Other Mediastinal Tumor-Like Conditions 267
Castleman's Disease 267
Index 274

TUMORS OF THE MEDIASTINUM

1
ANATOMY AND ANATOMIC COMPARTMENTS OF THE MEDIASTINUM

The mediastinum is a large compartment in the thoracic cavity, bounded laterally by the pleurae, anteriorly by the sternum, posteriorly by the vertebral column, superiorly by the thoracic inlet, and inferiorly by the diaphragm. It contains a large number of organs and structures. In clinical practice, the mediastinum is divided into four arbitrary portions: the superior, anterior, middle, and posterior compartments (fig. 1-1) (3). This division enables radiologists to localize lesions with accuracy and is valuable in the differential diagnosis of mediastinal lesions since certain cystic lesions and neoplasms occur preferentially in one compartment (fig. 1-2) (5).

NORMAL THYMUS GLAND

The thymus, one of the central lymphoid organs, plays an important role in cellular immunity by generating circulating T lymphocytes. Histologically, it is the prototype lymphoepithelial organ in that it consists of an intimate mixture of epithelial cells and lymphocytes (7), as well as other cell types important for the function of this organ. Recent advances in immunology, especially in the development of the immune system, have enhanced the knowledge about the function of the thymus and, to a certain extent, thymic tumors.

Embryology. In humans, thymic epithelium arises bilaterally from the third and probably fourth branchial pouches, which contain elements

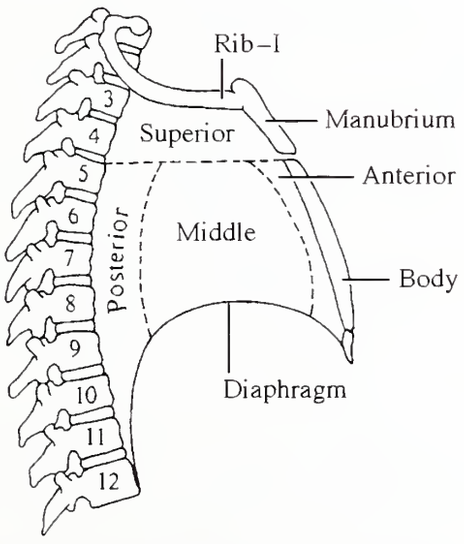


Figure 1-1
ANATOMIC COMPARTMENTS OF THE MEDIASTINUM

(Illustration from Pansky B. Review of gross anatomy. 6th ed. New York: McGraw-Hill, 1996:359.)

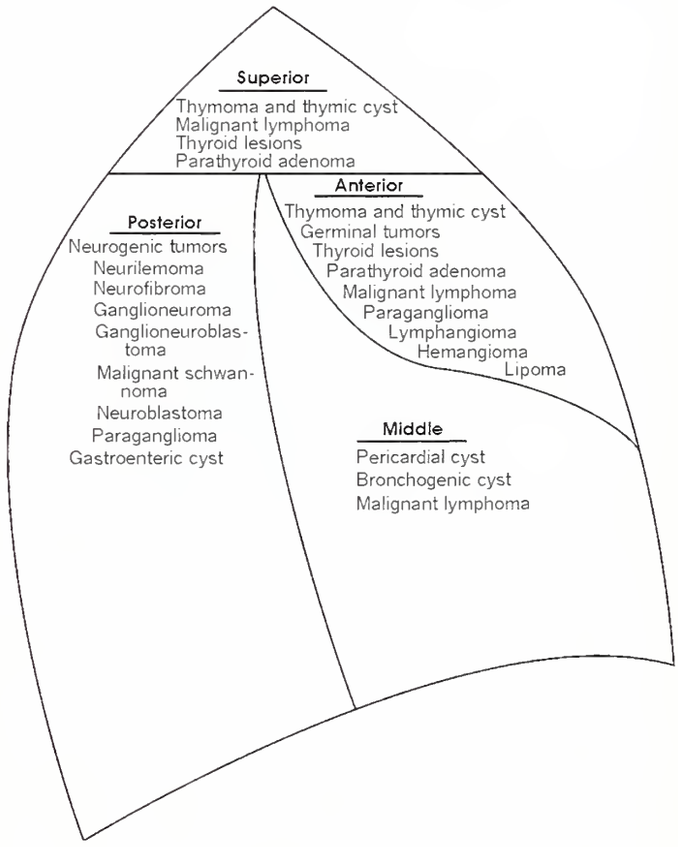


Figure 1-2
LOCATION OF MOST COMMON LESIONS OF THE MEDIASTINUM

(Fig. 8-1 from Rosai J. Ackerman's surgical pathology, 8th ed. St. Louis: CV Mosby, 1996:436.)

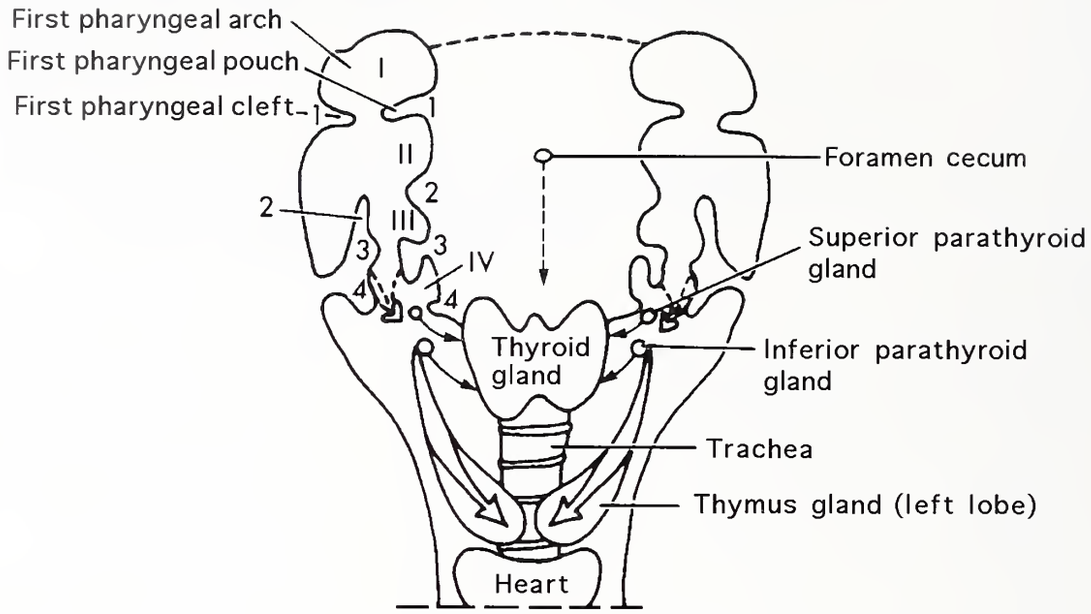


Figure 1-3
SCHEMATIC REPRESENTATION OF THYMIC EMBRYOGENESIS

The thymus gland originates from the pouch and cleft of the third pharyngeal structure. (Fig. 29-1 from Griffith RC. Thymus gland. In: Kissane JM, ed. Anderson's pathology. St. Louis: CV Mosby, 1990:1493–516.)

derived from all three germinal layers. Different clefts and pouches contribute to the thymus in other animals. Development begins in the sixth gestational week when paired cellular proliferations emerge from the third branchial cleft and from the endoderm of the ventral wing of the third pharyngeal pouch (fig. 1-3). The inferior parathyroid gland arises similarly from the dorsal wing of the pharyngeal pouch. Both primordia separate from the pharyngeal wall and begin their caudal migration into the anterosuperior mediastinum as epithelial tubules or cords. During this process, the ectoderm of the third branchial cleft covers the endodermally derived epithelium. The mesoderm provides vascular stroma and mesenchymal cells (1,3,7).

During the eighth week, the thymic primordia elongate caudally, forming two epithelial bars that fuse along the midline to occupy their final position within the anterosuperior mediastinum. During this migration, small fragments may separate from the primordia and persist postnatally along the migratory route, often in intimate connection with the inferior parathyroid gland (fig. 1-4) (6). Finally, they occupy their definitive position within the anterosuperior mediastinum. When the migration ends at the base of the heart, the thymus lies anteriorly to the great vessels in the superior mediastinum, with its upper poles extending laterally along the trachea into the base of the thyroid gland.

Until the ninth gestational week, the embryonic thymus remains as a purely epithelial organ. By the tenth week, small lymphoid cells originating in the fetal liver and bone marrow begin to migrate into the epithelial organ (1,2,7). Lobulation also occurs by the tenth week as a result of ingrowth of the capsule. The influx of lymphoid stem cells into the thymus occurs in successive waves. This is an active phenomenon that depends on the maturational state of the thymic epithelium. Differentiation of the thymus into cortex and medulla occurs as the lymphoid cells migrate into the thymic anlage. Inductive tissue interactions between the epithelial and mesenchymal components are necessary for the normal development of the thymus.

At this developmental stage, the epithelial cells at the periphery of the lobule become rounded, whereas those in the center appear more spindle shaped. Adjacent epithelial cells are connected by well-developed desmosomes. Other large mesenchymal cells are present at this time in the septa and among the central epithelial cells. These cells are histogenetically and functionally related to the interdigitating reticulum cells of thymus-dependent regions of peripheral lymphoid tissue. Macrophages colonize the thymus at the same stage as the lymphoid progenitors. Rare cells containing myofilaments, called myoid cells, are present in the central anlage as early as the eighth week. Erythroblasts, representing residua from

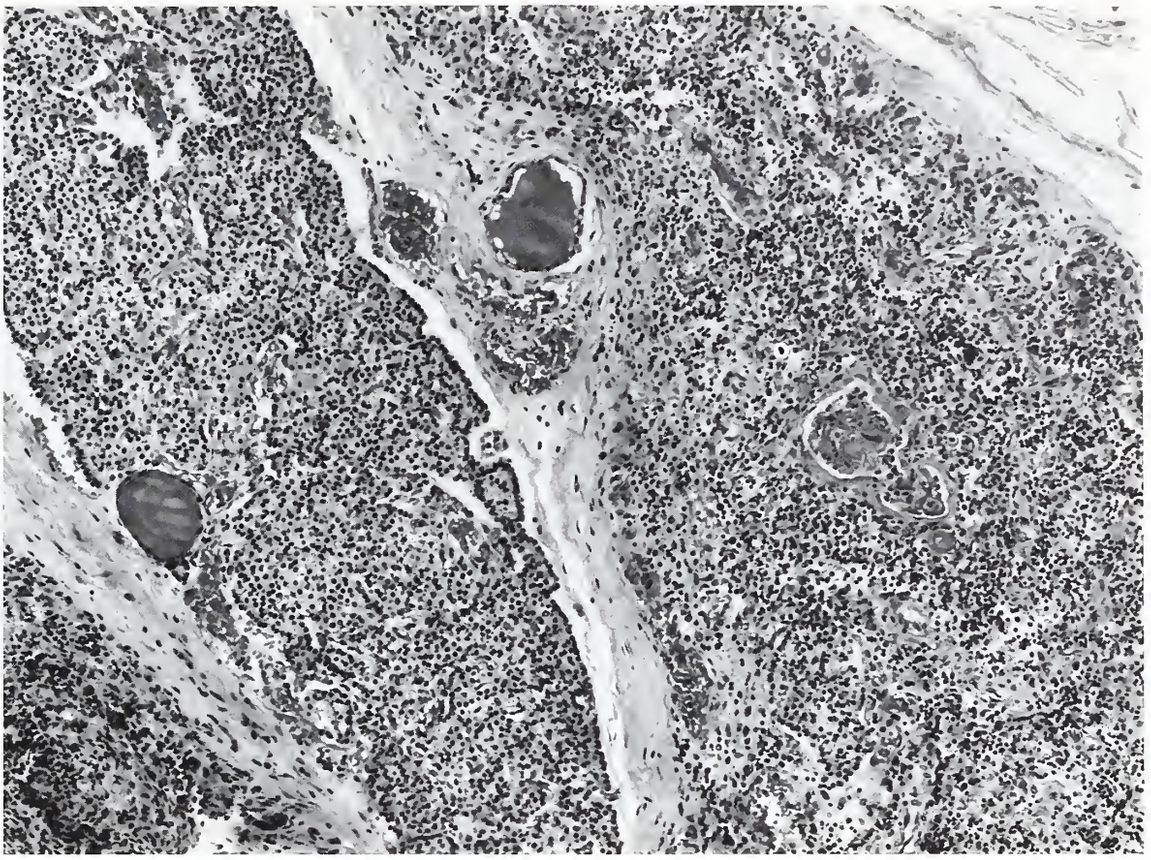


Figure 1-4
ECTOPIC THYMIC TISSUE SURROUNDING PARATHYROID GLAND
This may be called a parathymus: parathyroid tissue on the left side is surrounded by thymic tissue in which a Hassall corpuscle is seen.

earlier hematopoiesis in the primordial gland, may also be found.

Small tubular structures composed of epithelial cells are present in the central portion of the primordium. They become Hassall corpuscles at a later stage (7).

The development of the cortex and medulla is completed between the 14th and 16th gestational weeks. This morphologic differentiation is accompanied by phenotypic characterization of the epithelial cells and lymphocytes.

The thymus gland grows rapidly in embryonic life and attains its greatest weight in relation to body weight before birth, weighing an average of 15 g (1,3,6,7,11).

Location. The thymus is located predominantly in the anterosuperior mediastinum (fig. 1-5). Its base lies upon the pericardium and the great vessels. The upper pole of the each lobe extends into the neck and is joined to the lower pole of the corresponding lobe of the thyroid gland by the thyrothymic ligament. The lower

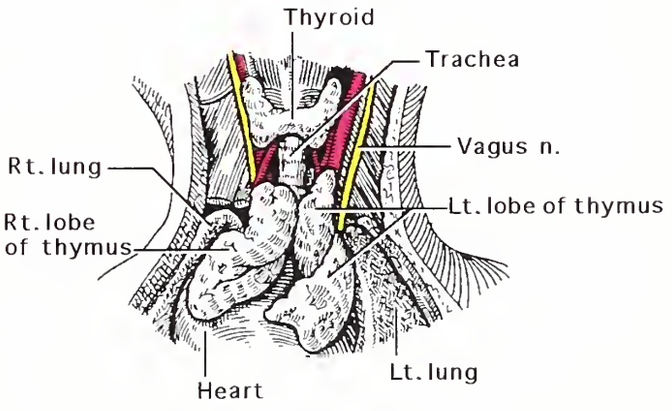


Figure 1-5
LOCATION OF THYMUS
(Illustration from Pansky B. Review of gross anatomy, 6th ed. New York: McGraw-Hill, 1996:359.)

poles of the thymic lobes extend down over the pericardium for a variable distance, usually to the level of the fourth costal cartilage.

The upper poles are closely applied to the trachea. The posterior boundary of the thymus

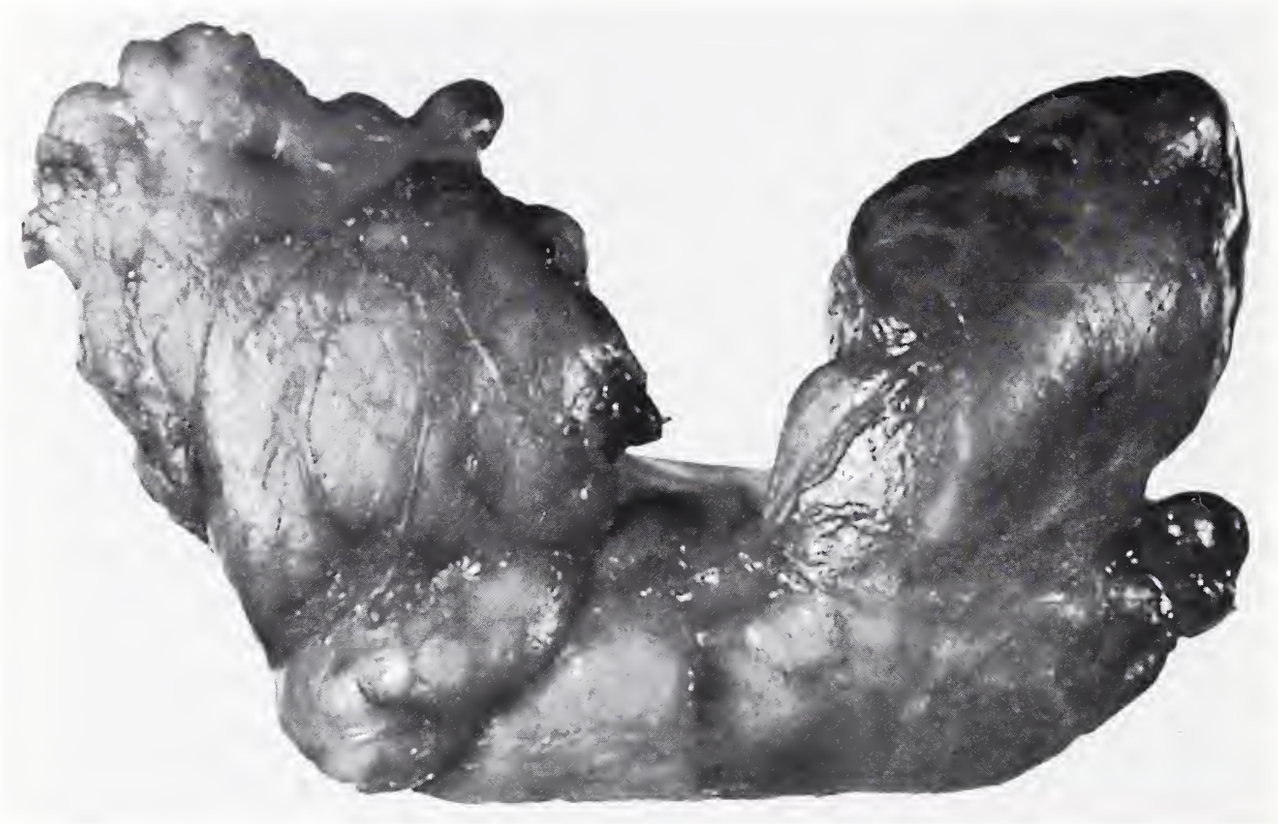


Figure 1-6
NORMAL THYMUS

Top: Infant thymus. Two separate lobes join at the lower poles. (Fig. 1-7 from Fascicle 13, 2nd Series.)

Right: Adult thymus. The thymus often shows an X- or H-shaped configuration.

is the pretracheal fascia, which separates it from the great vessels. Anteriorly, it is in contact with cervical fascia, strap muscles of the neck, the sternum, costal cartilages, and intercostal muscles. Reflections from the parietal pleura partially cover the lateral aspects of the gland.

Gross Features. The thymus is a pyramid-shaped organ composed of two fused lobes (fig. 1-6); each is completely covered by a fibrous capsule (6). The fully developed thymus is pink, which becomes gray following formalin fixation. It turns yellow with age involution, reflecting an increased deposition of mature fat. The vascularization of the thymus derives from branches of the inferior thyroid arteries, the internal mammary arteries, and the pericardiophrenic arteries. The innervation,

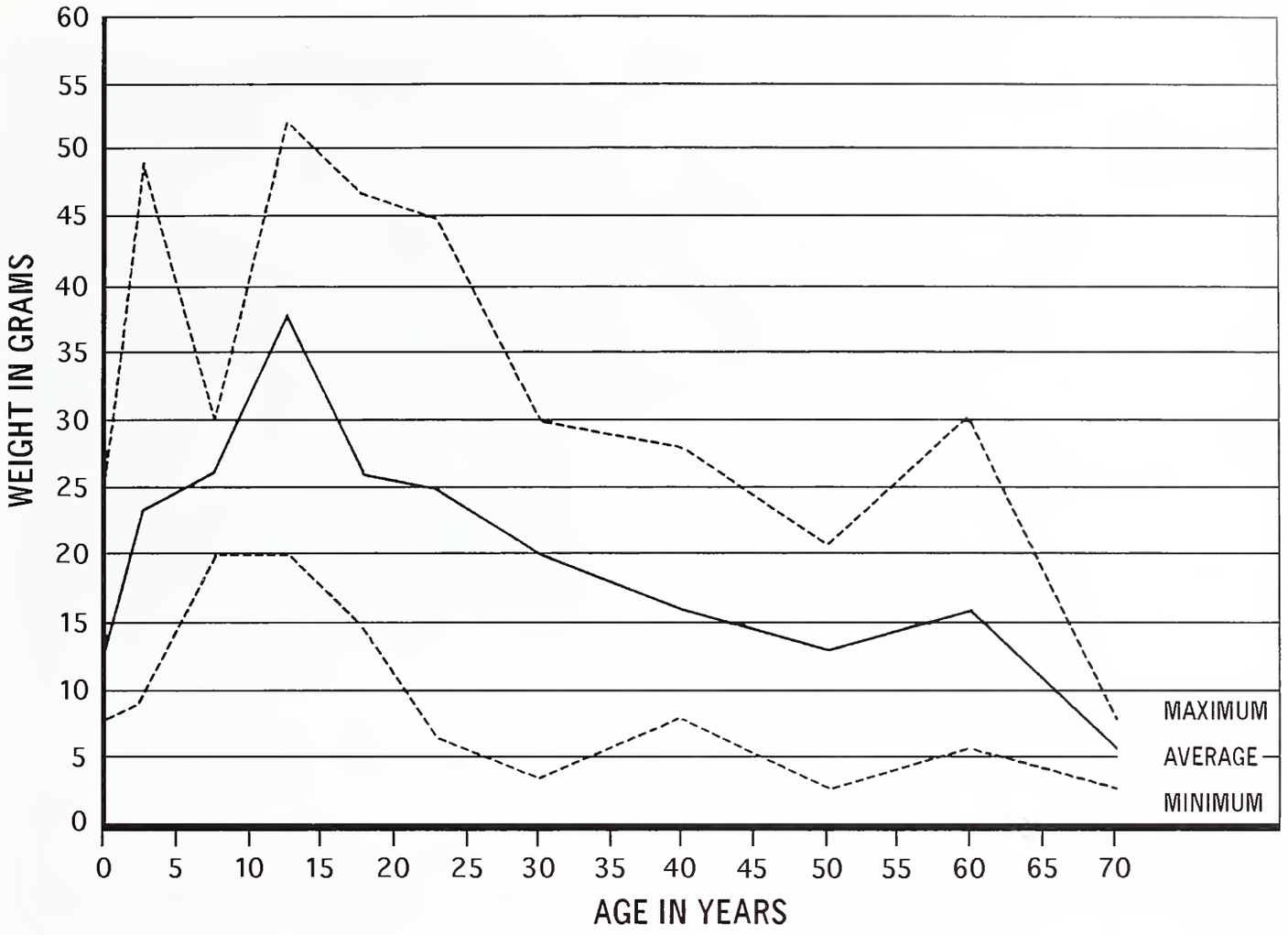


Figure 1-7
WEIGHT OF HUMAN THYMUS

Based on Hammar's data, variations in the weight of normal thymuses at any given age are shown. (Fig. 1-4 from Fascicle 19, 1st Series; graph 1 from Fascicle 13, 2nd Series.)

which is minimal and probably restricted to blood vessels, originates from the vagus nerve and cervical sympathetic nerves.

The size of the human thymus varies a great deal. There have been several studies in which the weight of the thymus was measured, but most were done many years ago and may not reflect the thymic weight at present. The weight of the normal thymus is mainly related to age: it is greatest in relation to body weight at the time of birth, weighing an average of 15 g. It continues to increase in size and weight until puberty to reach an average weight of 30 to 40 g (6,7,11). Subsequently, thymic weight declines during the process of aging involution and at 60 years of age is 10 to 15 g (fig. 1-7). Many conditions contribute to involution or enlargement of the thymus. Chronic stressful conditions cause involution. Death from asphyxia (largely in young persons) and several cardiovascular conditions are associated with higher than normal thymic weight (11) including myocardial fibrosis; coronary thrombosis, myocardial infarction, and ruptured myocardium; cor pulmonare; hypertensive heart disease with congestive heart failure; and coronary occlusion due to atheroma. The causal relationship between these conditions and increased thymic weight is unknown.

Microscopic Features. The thymus is divided into many small lobules by fibrous septa extending from the capsule (fig. 1-8). Each lobule measures from 0.5 to 2.0 mm and constitutes the basic structural unit of the gland. Each lobule is composed of two areas that can be clearly distinguished in histologic sections: cortex and medulla. The cortex appears darker because of its

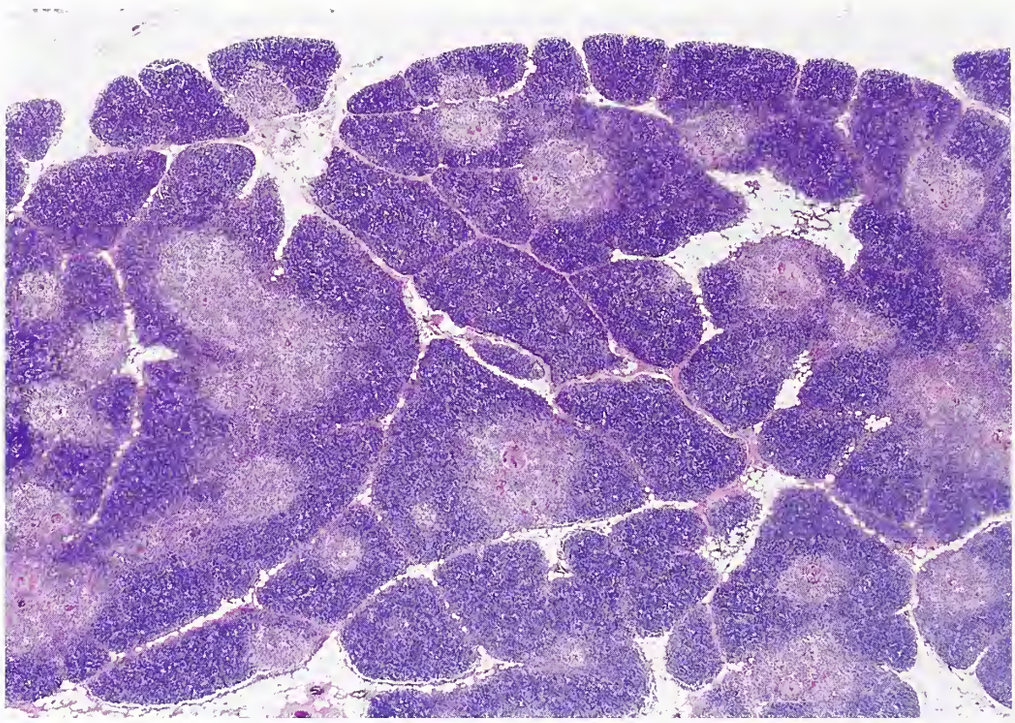


Figure 1-8
NORMAL THYMUS
Prominent lobulation by fibrofatty tissue septa is seen. Each lobule consists of dark cortex and pale medulla.

Table 1-1

DIFFERENTIAL CHARACTERISTICS OF CORTICAL AND MEDULLARY THYMIC EPITHELIAL CELLS UNDER LIGHT MICROSCOPY*

	Cortical	Medullary
Shape	Stellate	Spindle with cytoplasmic processes
Nucleus		
Shape	Oval-round	Oval-spindle, often with irregular contour
Size	Medium-large	Small-medium
Character	Thin and distinct nuclear membrane, very loose chromatin (clear nucleus)	Distinct nuclear membrane, finely distributed heterochromatin
Nucleolus	1, often prominent, round, central	+/-, little, not prominent
Cytoplasm	Scant, clear or faintly eosinophilic	Scant, eosinophilic, mostly seen in the cellular process
Cytoplasmic processes	Very thin, faintly eosinophilic	Long, thin, eosinophilic

*Table 3 from Müller-Hermelink HK, Marino M, Palestro G. Pathology of thymic epithelial tumors. In: Müller-Hermelink HK, ed. The human thymus. Current Top Pathol 1986;75:207–68.

population of lymphocytes, traditionally known as thymocytes (7). The thymocytes are admixed with a few epithelial and mesenchymal cells. Conversely, the medulla is lighter due to a fewer lymphocytes and more epithelial cells. The medullary portions are continuous from lobule to lobule, resulting in a highly branched stalk configuration.

Epithelial Cells. The epithelial cells of the thymus form the framework of the organ and are functionally essential for the maturation of T lymphocytes. They have been traditionally divided into cortical and medullary types on the basis of their location. Their cytologic features are distinct enough to be recognized by light microscopy (Table 1-1, fig. 1-9) (4).

Van de Wijngaert et al. (19) identified six types of thymic epithelial cells based on their ultrastructural features (Table 1-2, fig. 1-10). Types 2 and 3 are characterized by a special pattern of epithelium-lymphocyte interaction ("thymic nurse cells"), as demonstrated by the intracytoplasmic presence of lymphocytes.

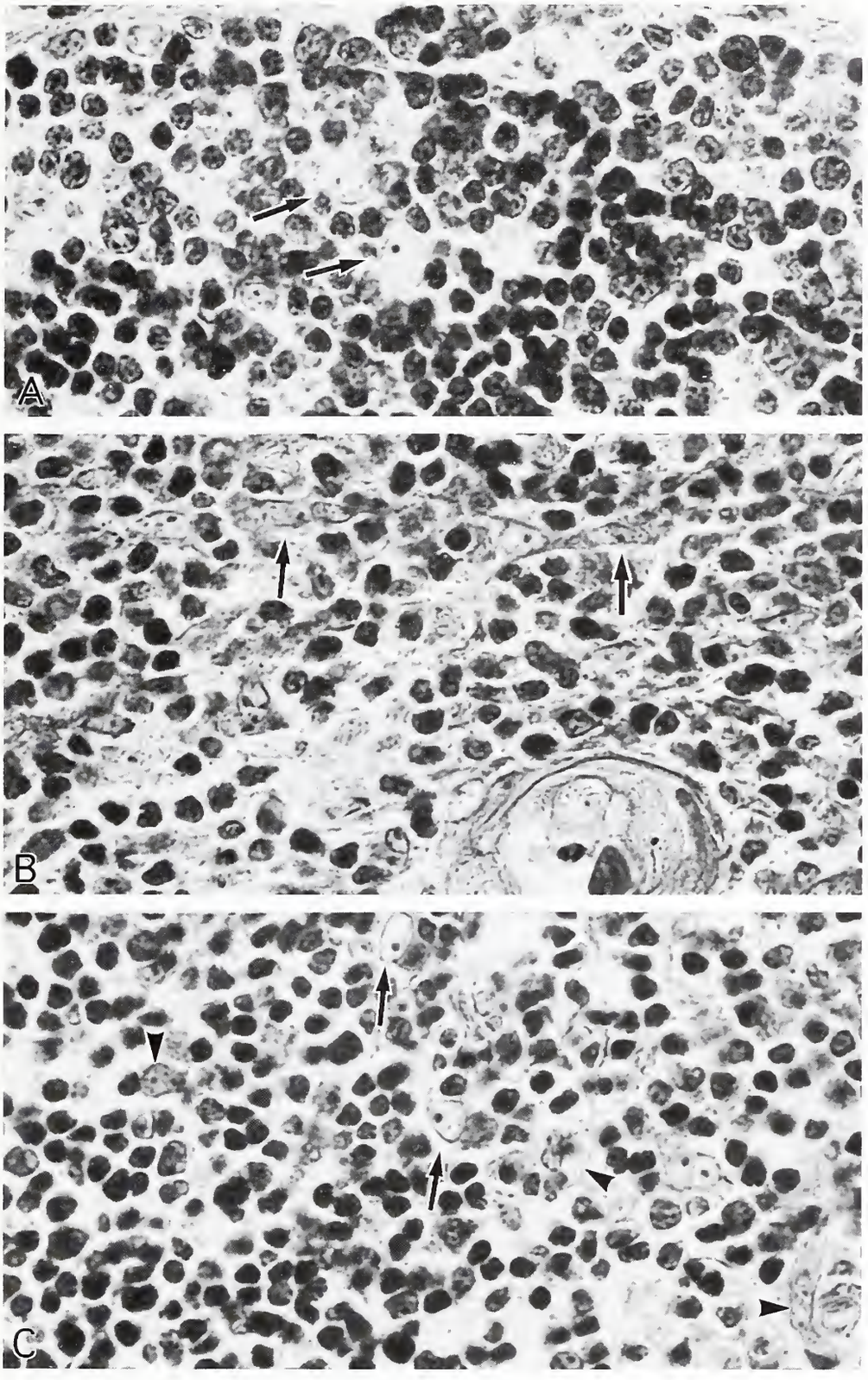


Figure 1-9
THYMIC EPITHELIAL CELLS

A: Cortex: epithelial cells (ECs) of cortical type have large, round to oval, clear nuclei and conspicuous nucleolus (arrows).

B: Medulla: fusiform ECs have spindle-shaped nucleus, coarse chromatin structure, and interconnecting cell processes. A Hassall corpuscle is seen in the right lower part.

C: Cortico-medullary junction: ECs of cortical type (arrows) and medullary type (arrowheads) are intermingled. (Fig. 1-2 from Müller-Hermelink HK, Marino M, Palestro G. Pathology of thymic epithelial tumors. In: Müller-Hermelink HK, ed. The human thymus. Current Top Pathol 1986;75:207–68.)

Recent immunohistochemical studies using various monoclonal antibodies against different antigens have also demonstrated heterogeneity of thymic epithelial cells (Tables 1-3, 1-4). Four to five different cell types have thus been described by differential expression of antigens (4,7). There has been an attempt to classify thymomas into cortical and medullary subtypes using a similar approach (4). This is discussed in detail in the chapter on thymoma.

Savino and Dardenne (16) noted differential expression of various cytokeratin (CK) types by epithelial cells in the cortex and medulla of the murine thymus. They described four cell types:

Table 1-2

MORPHOLOGIC CHARACTERISTICS AND LOCATION OF TYPES OF EPITHELIAL CELLS IN THE HUMAN THYMUS*

	Morphologic Characteristics	Location
Type 1 "subcapsular-perivascular"	Basal lamina, heterochromatic nucleus, long cisternae of RER, well-developed Golgi complex, micropinocytotic vesicles	Beneath capsule, around capillaries in cortex and cortico-medullary region
Type 2 "pale"	Round euchromatic nucleus, well-developed Golgi complex, short profiles of RER, electron-dense granules, tubular structures	Scattered in cortex and medulla, predominant in outer cortex
Type 3 "intermediate"	Spectrum in morphology between type 2 and type 4, euchromatic or heterochromatic irregularly shaped nucleus, dilated cisternae of nucleus and RER	Mid-cortex, deep cortex, medulla
Type 4 "dark"	Heterochromatic, electron-dense, irregularly shaped nucleus; dilated cisternae of nucleus and RER; residual bodies; swollen mitochondria	Deep cortex, scattered in medulla and around Hassall corpuscles
Type 5 "undifferentiated"	Rounded nucleus with some heterochromatin, polyribosomes, small bundles of tonofilaments, small desmosomes	In groups in cortico-medullary region, scattered in medulla
Type 6 "large-medullary"	Large, rounded nucleus, either eu- or heterochromatic; sometimes RER well developed; abundant tonofilaments; tubular structures	Scattered in medulla, adjacent to large Hassall corpuscles, part of small Hassall corpuscles

*Table 1 from van de Wijngaert FP, Kendall MD, Schuurman HJ, Rademakers LH, Karter K. Heterogeneity of epithelial cells in the human thymus. An ultrastructural study. Cell Tissue Res 1984;237:227–37.

cortical epithelial cell (CK8 and CK18 positive; CK19 and CK3/10 negative); a subset of medullary epithelial cells reactive with only a polyclonal antikeratin antibody but nonreactive with monoclonal antibodies against CK8, CK18, CK19, CK3/10; another subset of medullary epithelial cells positive for CK19 but negative for CK8, CK18, and CK3/10; and epithelial cells of Hassall corpuscles positive for CK3/10 but negative for CK8, CK18, and CK19 (fig. 1-11). In humans, the differential expression of different cytokeratins is not as distinct as in the mouse (fig. 1-12) (9).

Hassall Corpuscles. Hassall corpuscles are characteristic structures of the thymus (fig. 1-13). They are present exclusively in the medulla and recognized as round keratinized formations. They show a concentric arrangement of the mature epithelial cells and a keratinized center, which is often calcified. The periphery of the corpuscle is continuous with the medullary epithelial cells from which it is derived. Hassall corpuscles may show secondary changes such as central cystic change, with accumulation of cellular debris and inflammatory cells (fig. 1-14) (7). Marked cystic change may result in so-called multilocular thymic cyst, a condition which had been regarded as a congenital abnormality previously but may be instead the result of cystic enlargement of Hassall corpuscles resulting from acquired inflammatory changes in the thymus. The presence of columnar epithelium-lined cysts may also be related to the cystic change of the Hassall corpuscles (7). This columnar epithelium probably derives from the remnant of the pharyngeal pouch from which the thymus originates.

Thymic Hormones. The production of thymic hormones by the thymic epithelial cells is allegedly responsible for the regulation of T-lymphocyte development. A large body of literature has accumulated describing the isolation, purification, characterization, and functional properties of different macromolecules, some of which have been synthesized (17). The better known are thymosin 1, thymulin, thymopoietin, thymic humoral factor,

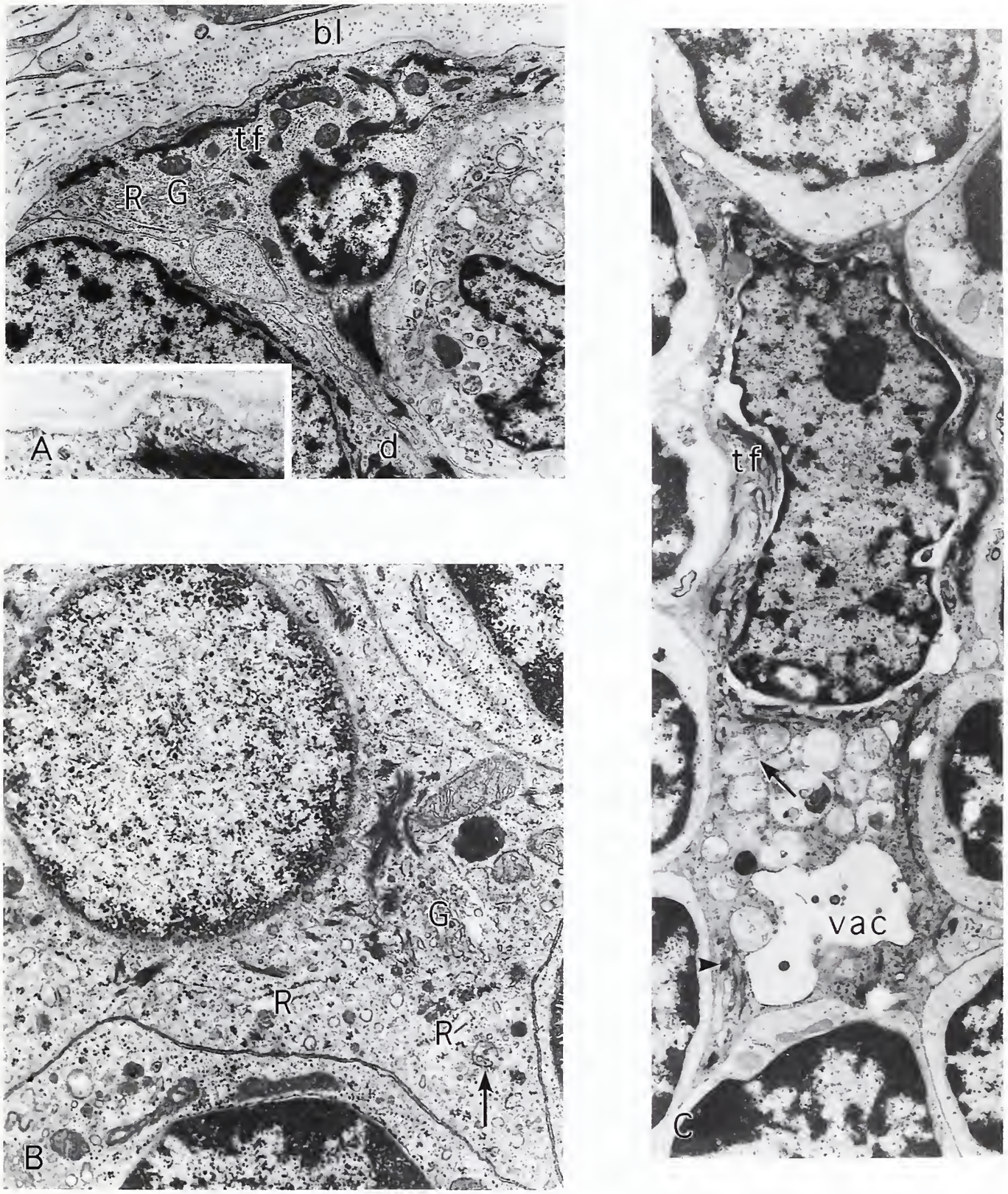


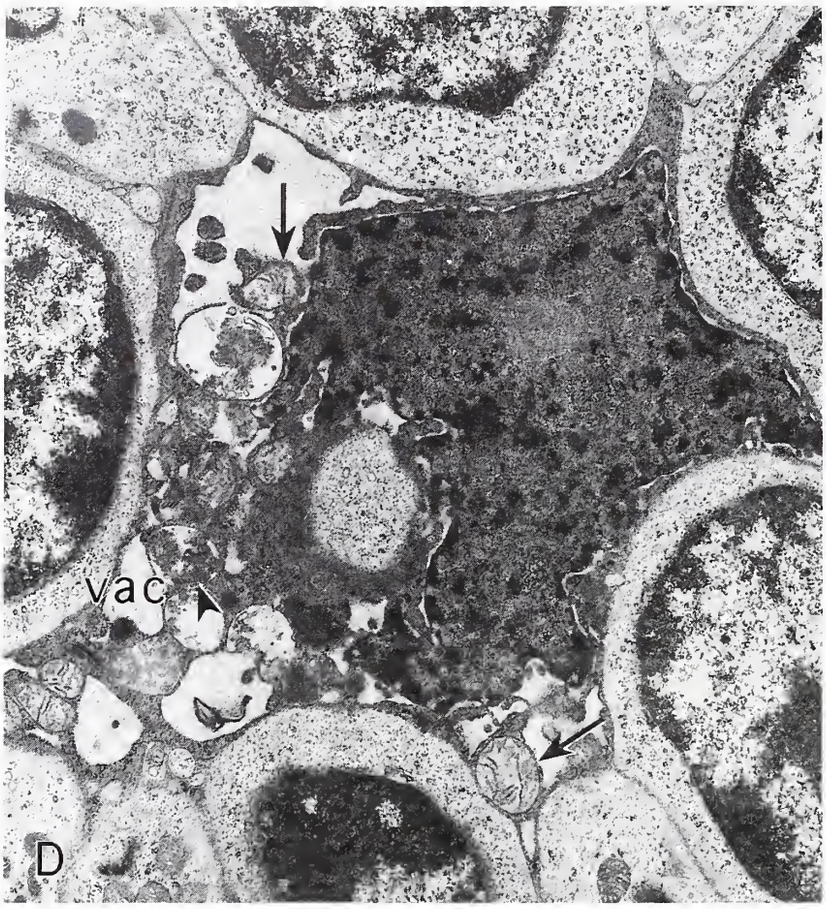
Figure 1-10
ELECTRON MICROSCOPY OF THYMIC EPITHELIAL CELLS

Six types of cells are identified.

A: Type 1 "subcapsular-perivascular" epithelial cell (6 1/2-year-old donor). R: cisternae of RER; G: a Golgi complex; d: desmosomes; bl: basal lamina; tf: tonofilaments (X8,000). Inset: Higher magnification of part of a cell showing micropinocytotic vesicles facing the basal lumina (X25,000).

B: Type 2 "pale" epithelial cell in the outer cortex. R: profiles of RER; G: a Golgi complex; arrow: multivesicular body (X8,000).

C: Type 3 "intermediate" epithelial cell in the cortex. Dilated nuclear cisternum is seen. tf: tonofilaments; vac: vacuoles; arrowhead: desmosome; arrow: swollen mitochondria (X9,000).



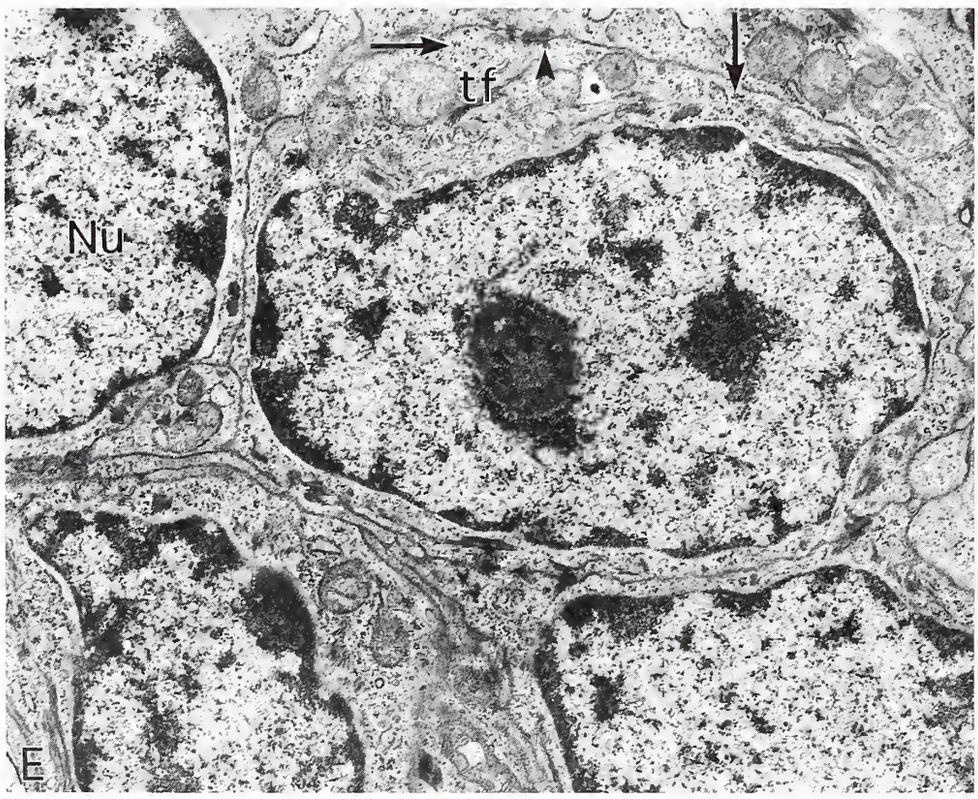


Figure 1-10 (Continued)
ELECTRON MICROSCOPY OF THYMIC EPITHELIAL CELLS

D: Type 4 "dark" epithelial cell in the deep cortex. Nuclear cisternum is dilated. Vac: vacuoles; arrow: swollen mitochondria; arrowhead: residual bodies (X12,000).

E: Type 5 "undifferentiated" epithelial cell in the cortico-medullary region. Nu: nucleus; tf: tonofilaments; arrowhead: desmosome; arrow: polyribosome (X18,000).

Figure 1-10 (Continued)

F: Two type 6 "large medullary" epithelial cells (6) adjacent to a Hassall corpuscle and two type 4 epithelial cells (4) in the medulla (X7,000). (A, E, F: Figs. 2, 4, 5 from Kendall MD, van de Wijngaert FP, Shuurman HJ, Rademakers LH, Kater L. Heterogeneity of the human epithelial microenvironment at the ultrastructural level. In: Klaus GG ed., Microenvironments in the lymphoid system. Advances in experimental medicine and biology, Vol 186, New York: Plenum Press, 1985;189–97. B, C, D: Figs 5, 6, 8 from van de Wijngaert FP, Kendall MD, Shuurman HJ, Rademakers LH, Kater L. Heterogeneity of epithelial cells in the human thymus. An ultrastructural study. Cell Tissue Res 1984;237:227–37.)

and serum thymic factor. In some reports, hormone production has been localized to the subcapsular cortical and medullary epithelial cells (7). This finding has led to the suggestion that these two cell subtypes represent the functional (secretory or "endocrine") portion of the thymus, as contrasted to the nonsecretory epithelium of the inner cortex and Hassall corpuscles. An immunohistochemical study using antibodies against thymosins 1 and 3 showed the high specificity of these antibodies for recognition of the epithelial cells of the normal thymus and thymoma (10). Application of these antibodies for differential diagnosis of thymic epithelial tumors may be useful but additional data are required.

Some thymic hormones have been used to treat patients with immunodeficiency, malignancy, viral and fungal infections, and autoimmune disorders (8,17). Results from these trials are encouraging but they are still in an experimental stage.

Lymphocytes (Thymocytes). The thymic cortex is densely populated by lymphocytes of various sizes. Mitotically active prothymocytes or large lymphoblasts comprise about 10 to 15 percent of the lymphoid cells in the thymus and are found predominantly in the subcapsular portion of the outer cortex (4,7). A gradient of smaller, less mitotically active lymphocytes is seen in the outer cortex, into the deep cortex, into the cortical medullary junction, and into the medulla. The term thymocyte was used originally to designate all lymphocytes in the thymus. Recently the term has been restricted to indicate the immature T lymphocytes in the thymus.

Table 1-3

LIST OF ANTIBODIES COMMONLY USED FOR ANALYSIS OF THYMIC MICROANATOMY*

Antibody	Clones or Producer Animal	mc/pc**	Antigen or Cells Identified	Source
Anti-HLA-A,B,C	61D2	mc	Major serologically defined antigens HLA-A,B,C	Bethesda Research Laboratories, Neu-Isenburg, FRG
Anti-HLA-DR	7.2	mc	HLA-DR antigens (Ia-like, p28, 33)	New England Nuclear, Dreieich, FRG
Ki-M3	Balb/c mouse	mc	Monocytes and subpopulations of macrophages, all thymic epithelial cells	Radzun and Parwaresch (1983) Cell Immunol 82:174
21A6	Balb/c mouse	mc	Cortical epithelial cells of thymus, some nonlymphoid cells in human tonsil	Gift of Dr. Harpprecht and Dr. Westphal, University of Kiel, FRG
IV/82	Balb/c mouse	mc	Squamous epithelium, keratin	Pathology Institute, Kiel, FRG
34βE12	Balb/c mouse	mc	57/66kd† keratins in squamous epithelium, ductal epithelium, and parabasal glandular cells	Gown and Vogel (1982) J Cell Biol 95:414
35βH11	Balb/c mouse	mc	54kd† keratin(s) in most non-squamous epithelia	Gown and Vogel (1982) J Cell Biol 95:414
Anti-FTS	2H2H4-IgG2a	mc	*Facteur thymique sérique*	Dardenne et al. (1982) Immunology 4:73
Anti-FTS	1H6H10-IgG1	mc	*Facteur thymique sérique*	Dardenne et al. (1982) Immunology 4:73
Anti-Ep-1	F6B6	mc	Ep-1: epithelial cells	Dr. M. Dardenne, Paris, France
Anti-α-meten-kephalin	Rabbit	pc	Methionine enkephalin in rat globus pallidus and spinal cord	Immuno Nuclear Corporation, Stillwater, MN
Ki-M1	Balb/c mouse	mc	Monocytes and macrophages	Radzun and Parwaresch (1983) Cell Immunol 82:174
Ki-M6	Balb/c mouse	mc	Monocytes and macrophages	Dr. Radzun, Kiel, FRG
Anti-Leu1	L17/F12	mc	All T cells (gp 67)	Becton-Dickinson, Oxnard, CA
Anti-Leu2a	SK1	mc	Suppressor/cytotoxic subset of T cells	Dr. R. Evans, New York, NY
Anti-Leu3a	SK3	mc	Helper/inducer subset of T cells	Dr. R. Evans, New York, NY
Anti-Leu4	SK7	mc	Sheep erythrocyte receptor-positive T cells	Becton-Dickinson, Oxnard, CA
Anti-Leu6	SK9	mc	Common thymocytes, IDCs,‡ and Langerhans cells of the skin	Dr. R. Evans, New York, NY
OKT6	OKT6	mc	Human common thymocytes	Ortho Diagnostic System, Inc. Raritan, NJ
Anti-TdT§	Rabbit	pc	Terminal deoxynucleotidyl transferase	Supertechs, Rockville, MD

*Table 1 from Müller-Hermelink HK, Marino M, Palestro G. Pathology of thymic epithelial tumors. In: Müller-Hermelink HK, ed. The human thymus. Current Top Pathol 1986;75:207–68.
**mc: monoclonal; pc: polyclonal.
†Molecular weight of keratin polypeptide.
‡IDC: interdigitating reticulum cell.
§Added in this table.

Table 1-4

IMMUNOHISTOCHEMICAL REACTIVITY OF NONLYMPHOID CELLS IN HUMAN THYMUS*

	Ki-M3	HLA-DR	HLA-A,B,C	21 A6	IV/82	34β E12	35β H11	FTS	Ep-1	α-Meten-kephalin	Ki-M1	Ki-M6
Epithelial cells												
Surface epithelium	+	–	–	–	+	+	+	+	+	+	–	–
Perivascular epithelium	+	–	–	–	+	+	+	+	+	+	–	–
Subcortical epithelium	+	+	+	+	–	–	+	–	–	–	–	–
Medullary epithelium	+	+	+	–	+	+	+	+	+	+	–	–
Hassall corpuscles	–	–	+	–	–**	+	–	–	–	–	–	–
Other nonlymphoid cells												
Interdigitating reticulum cells (IDCs)	–	+	+	–	–	–	–	–	–	–	+	–
Macrophages	+/–	+	+	–	–	–	–	–	–	–	+	+

*Table 2 from Müller-Hermelink HK, Marino M, Palestro G. Pathology of thymic epithelial tumors. In: Müller-Hermelink HK, ed. The human thymus. Current Top Pathol 1986;75:207–68.
**Only the peripheral part is stained.

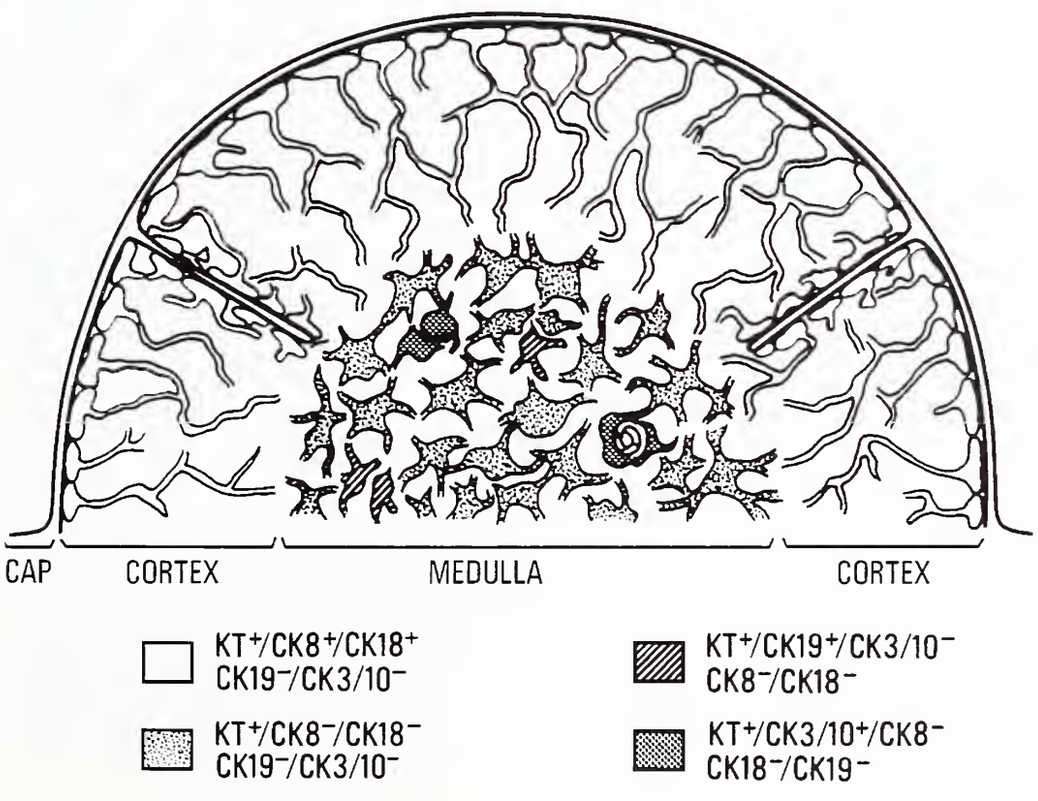


Figure 1-11
SCHEMATIC REPRESENTATION OF CYTOKERATIN EXPRESSION BY EPITHELIAL CELLS OF MOUSE THYMUS
(Fig. 1-5 from Savino W, Dardenne M. Developmental studies on expression of monoclonal antibody-defined cytokeratins by thymic epithelial cells from normal and autoimmune mice. J Histochem Cytochem 1988;36:1123–9.)

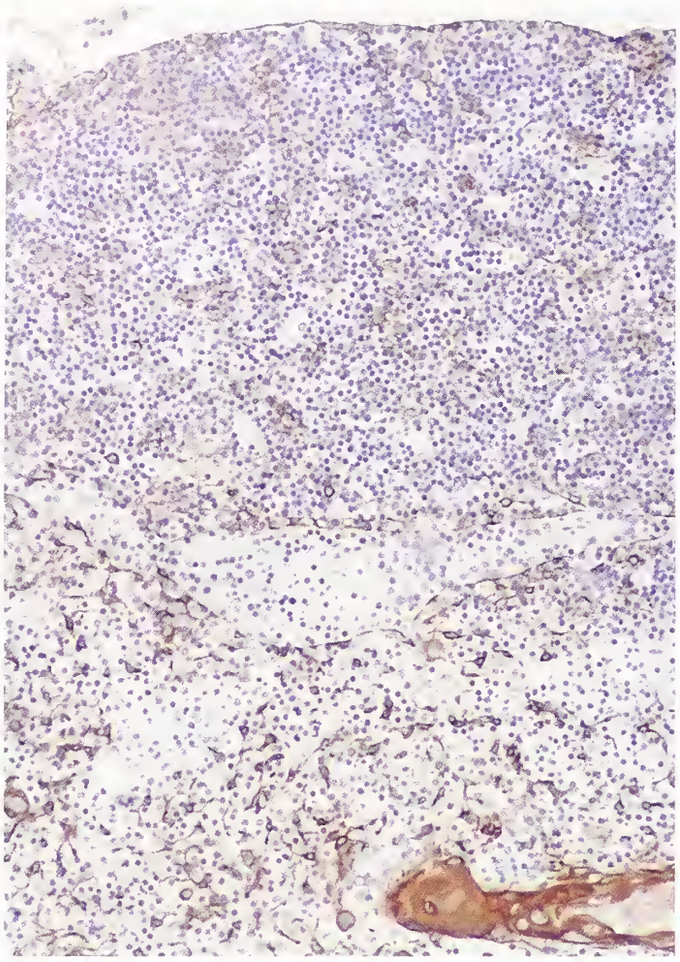


Figure 1-12
EXPRESSION OF CYTOKERATIN 19
IN HUMAN THYMUS
Epithelial cells of cortex and medulla, including those of a Hassall corpuscle, are equally positive for CK19.

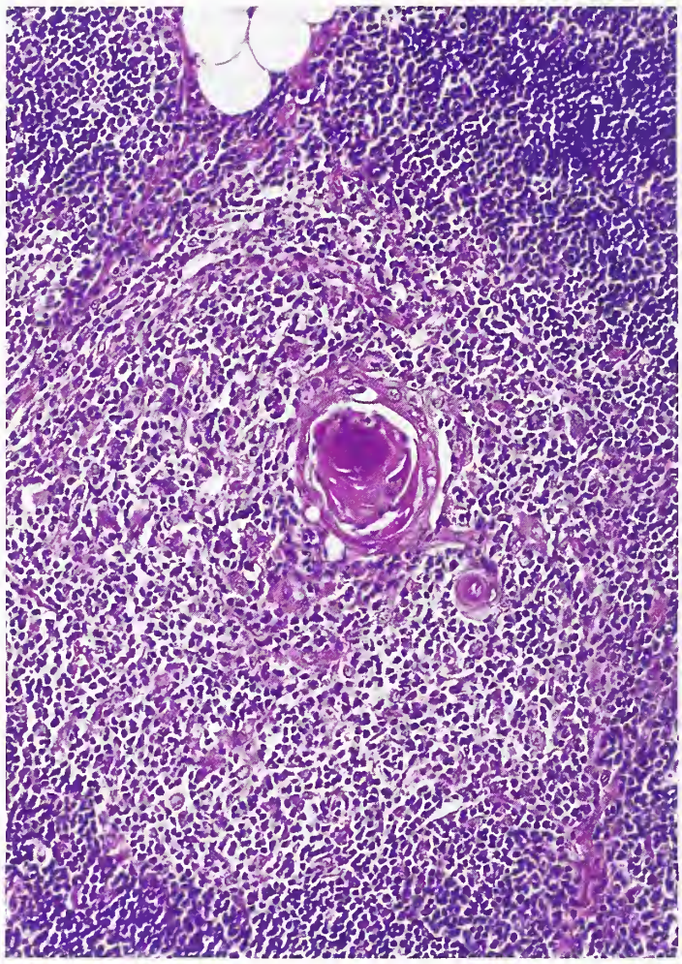


Figure 1-13
HASSALL CORPUSCLE
A Hassall corpuscle with a granular layer is present in the medulla, and displays keratinization.

In the cortex, intense lymphopoiesis, lympholysis, and active phagocytosis are indicative of extensive ineffective lymphopoiesis (probably 99 percent of thymocytes die in situ). This results in a prominent starry sky appearance in the active thymus (7).

Other Cell Types. In addition to epithelial cells and lymphocytes of T-cell lineage, the thymus contains a variety of cell types (7,20). B lymphocytes can be found either as lymphoid follicles with germinal centers in the septa or scattered in the medulla (fig. 1-15). The presence of germinal centers in the perivascular space led to the proposal that the thymus may be divided into two major compartments: the cortex and medulla composing the true thymic parenchyma, and the extraparenchymal compartment comprised by the perivascular spaces of the thymus (7). A germinal center occurs in the thymus of 2 to 40 percent of normal individuals. This wide variation may be related to a sampling factor or to the age of the patients. Germinal centers are especially common in children and adolescents.

Macrophages are mainly present in the cortex but also occur in the medulla (fig. 1-16) (15). They are functionally active and show strong lysosomal enzyme activity. Interdigitating reticulum cells are numerous in the medulla and at the cortico-medullary junction (fig. 1-17) (13,15). They are positive for S-100 protein and have little lysosomal enzyme activity. Both of these cells express class I and class II MHC antigens, have attributes of antigen-presenting cells, and play an important role in the clonal expansion of T lymphocytes. Langerhans cells have also been identified in the thymic medulla. Eosinophiles, mast cells, and plasma cells are present in the connective tissue septa of the thymus.

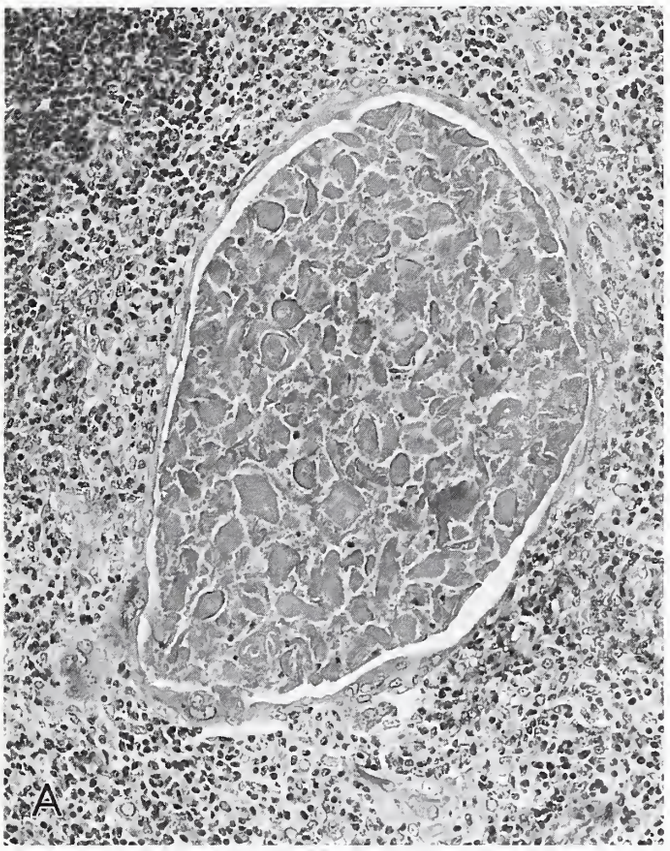
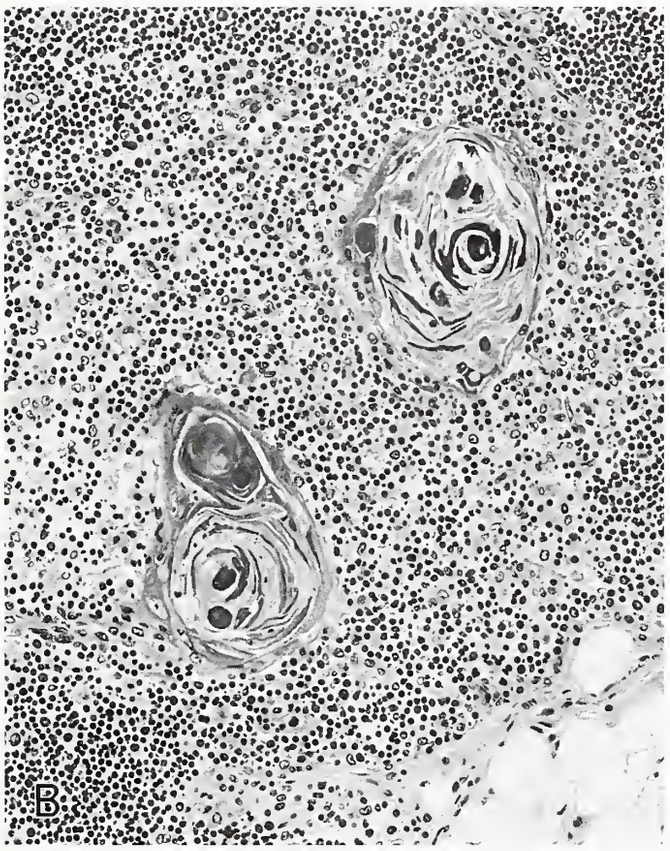


Figure 1-14
DEGENERATIVE CHANGE
IN HASSALL CORPUSCLES

A: Cystic dilatation with accumulation of cellular debris and a few inflammatory cells.

B: Dystrophic calcification.

C: Accumulation of mucoid substances with microcystic changes.



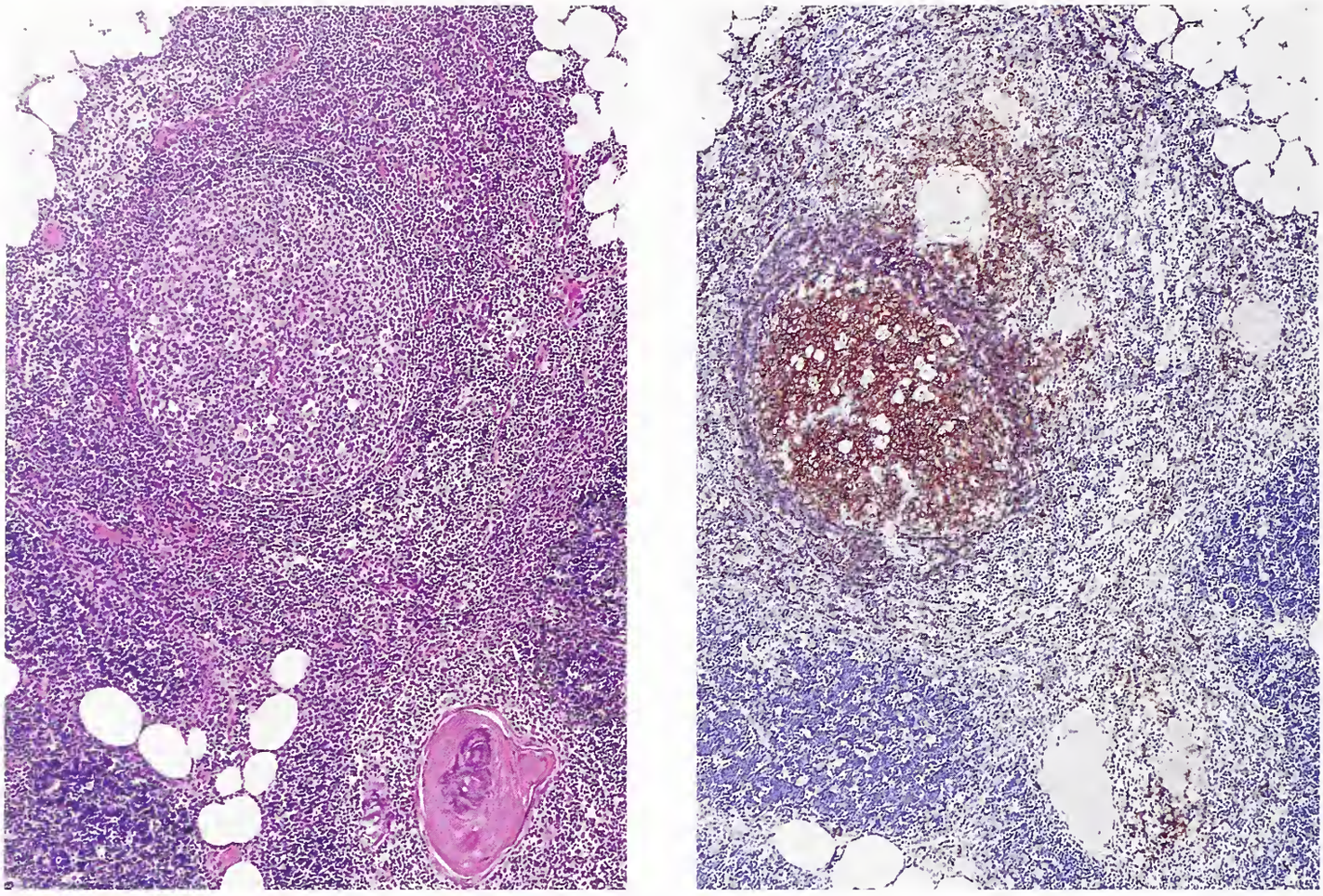


Figure 1-15
PRESENCE OF B-CELL FOLLICLE WITH GERMINAL CENTER

Hematoxylin and eosin stain (left) and immunohistochemical stain with L26 antibody (right). B cells are also scattered in the medulla.

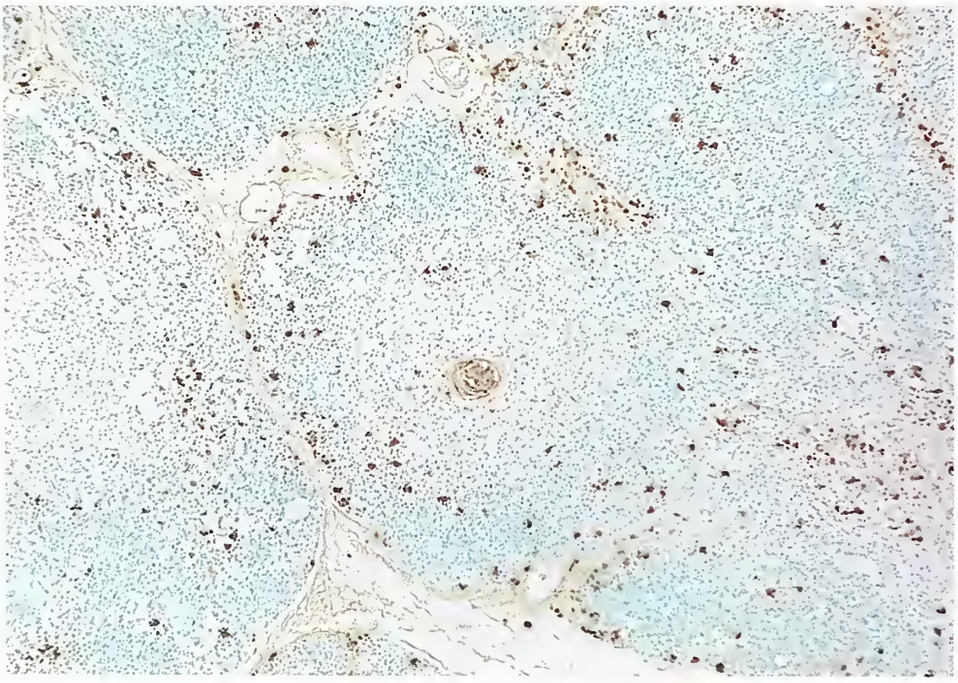


Figure 1-16
DISTRIBUTION
OF MACROPHAGES

Most lysozyme-positive macrophages are present in the cortex, especially in the subcapsular or subseptal region. A few macrophages are also present in the medulla. (Immunohistochemical staining of lysozyme)

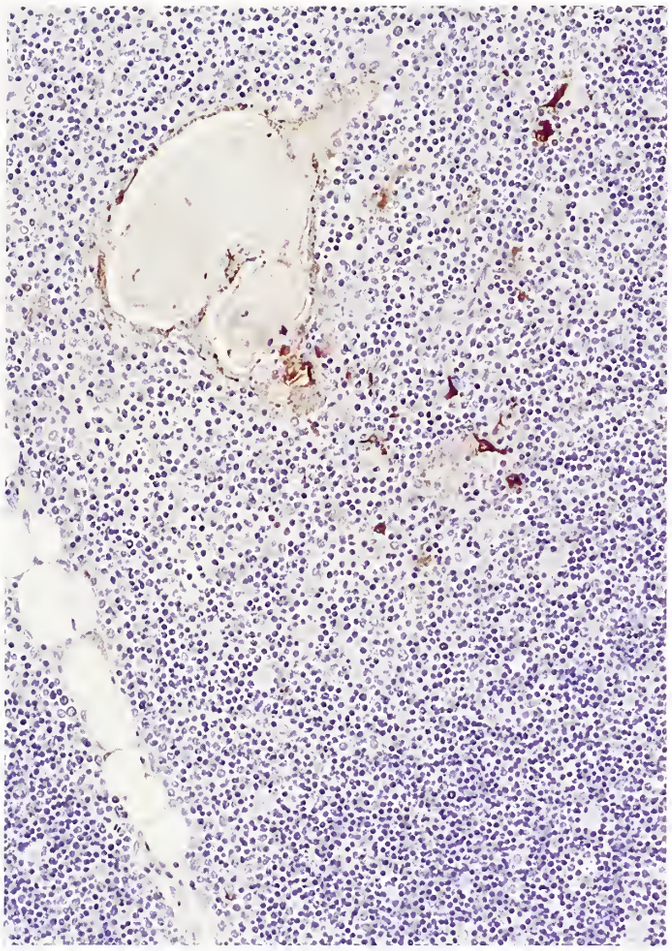


Figure 1-17
DISTRIBUTION OF INTERDIGITATING RETICULUM CELLS
S-100–positive cells are present in the medulla. (Immunohistochemical staining of S-100)

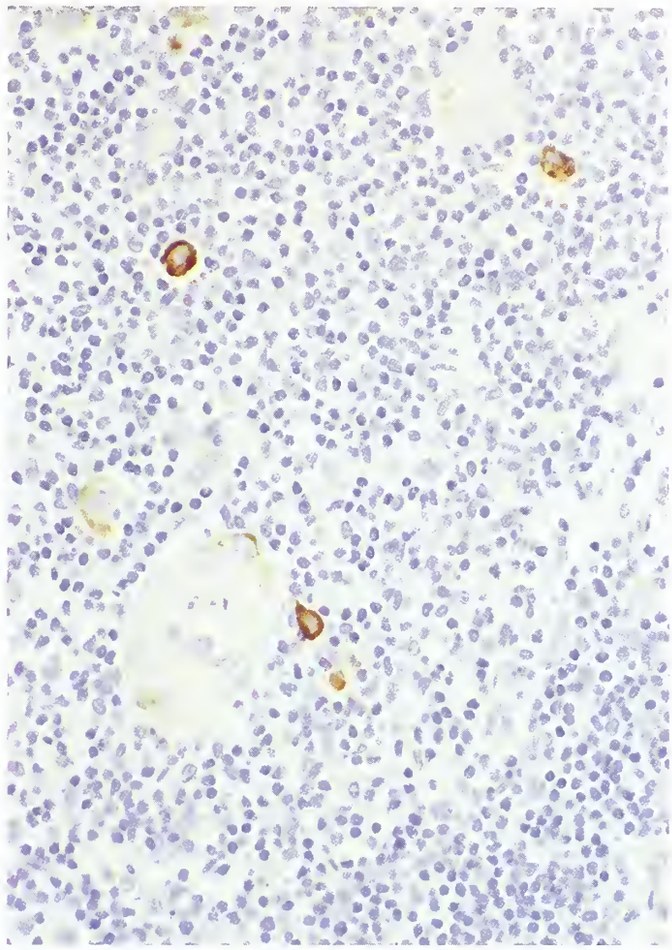


Figure 1-18
MYOID CELLS IN THE MEDULLA
Desmin-positive cells are present in close proximity to Hassall corpuscles. (Immunohistochemical staining of desmin)

Myoid or striated cells are located in the medulla (fig. 1-18) (1,7). They are prominent in the thymus of birds and reptiles but can also be found in the human thymus. They are located in small groups adjacent to Hassall corpuscles and are more frequent in newborns. Myoid cells are identical to striated muscle cells by immunohistochemical and ultrastructural criteria. The histogenesis of myoid cells remains a subject of debate. Although the myoid cells are in close proximity to the thymic epithelial cells, evidence is lacking that these cells are derived from epithelial cells. Some investigators favor a neural crest origin for this cell type (14). Myoid cells are of great interest because of their potential role in the pathogenesis of myasthenia gravis. Connective tissue elements of the thymus include vessels, fibrous tissue, nerves, and fat.

Maturation of Thymocytes. The thymus provides the essential microenvironment for the differentiation and expansion of T-lymphocyte subpopulations. The process of T-lymphocyte expansion is an essential component of the complex network of immunoregulatory and cell-mediated effector functions.

The lymphoid population of the thymus has been shown to exhibit a marked immunophenotypic heterogeneity, reflecting its functional diversity. The process of T-cell differentiation begins after hematopoietic progenitor cells, the prothymocytes, migrate from the bone marrow to the subcapsular area of the thymus, and involves an intrathymic migration through a theoretical cellular microenvironment from the cortex to the medulla (12). During this process interactions between the developing thymocytes and stromal thymic epithelial cells occur.

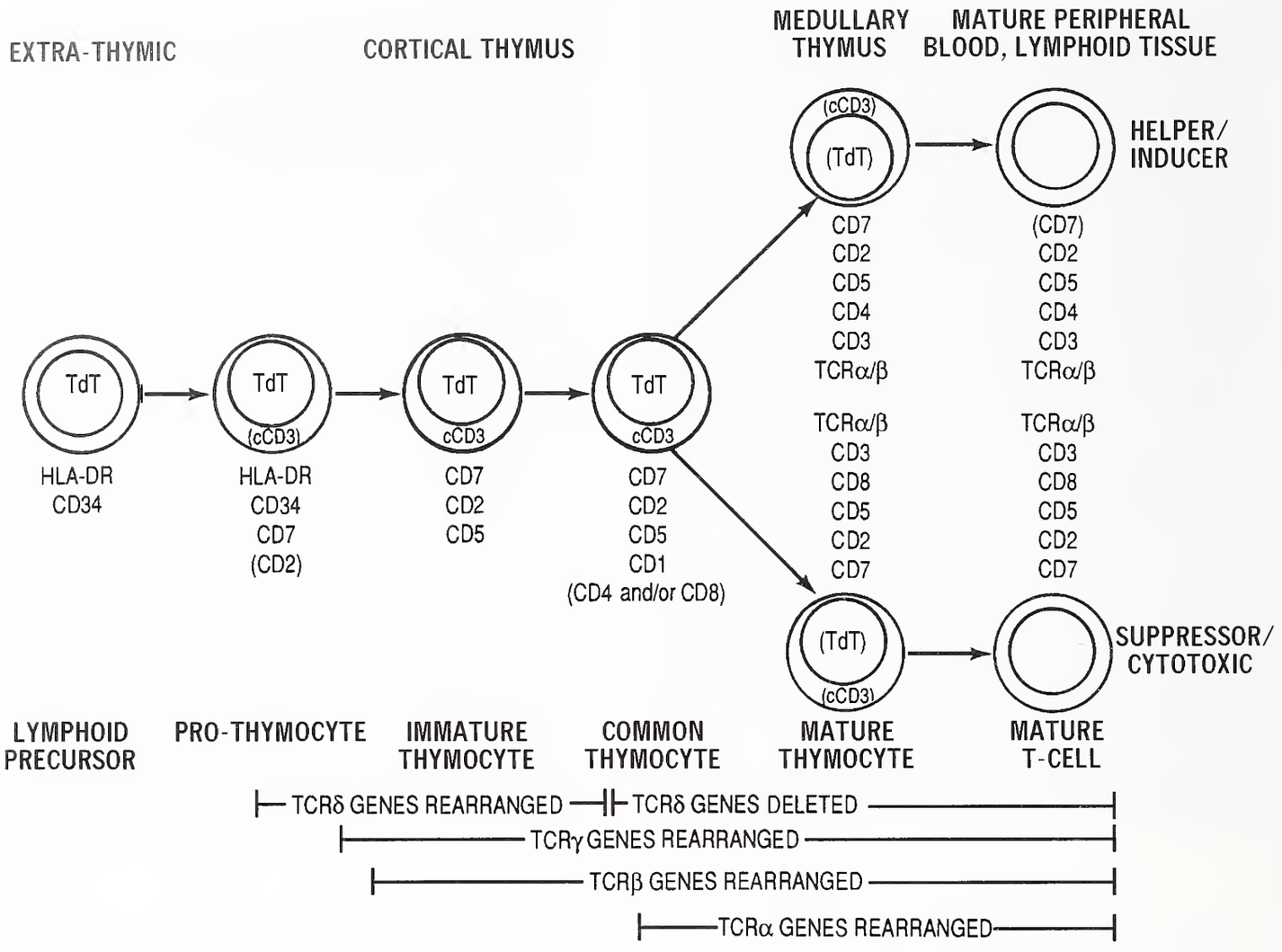


Figure 1-19
SCHEMATIC REPRESENTATION OF T-CELL ONTOGENY

The parentheses indicate that only a subpopulation of these cells expresses this marker. (Fig. 3.40 from Knowles DM, Chadburn A, Inghirami G. Immunophenotypic markers useful in the diagnosis and classification of hematopoietic neoplasms. In: Knowles DM, ed. Neoplastic hematopathology. Baltimore: Williams & Wilkins, 1992:73–167.)

Thymic nurse cell–thymocyte interaction is believed to be an essential step in this process (2). At the end of this maturation gradient, thymocytes with essentially mature phenotypes exit through the thymus to the peripheral lymphatic compartment, where functional diversification is completed.

The intrathymic portion of the T-cell maturation has been divided empirically into three stages (fig. 1-19) (7,12). As the thymocytes encounter the various inductive, hormonal, and proliferative signals from various subpopulations of subcortical and cortical epithelial cells and interdigitating reticulum cells, genes, enzymes, and surface receptor molecules are activated. This differential expression of genes identifies thymocytes in each developmental stage. Although the molecular events operative at the early stage of thymocyte development are not completely understood, it is now appreciated that genes that encode the T-cell antigen receptors and other important surface molecules of the thymocytes interact with epithelial MHC antigens. The result of these interactions is a clonal selection for the T-lymphocyte antigen receptors that distinguishes self from nonself.

Involution. The thymus normally decreases in size and weight with advancing age. This process of involution starts at puberty, at which time the organ reaches its maximum absolute weight (1,3,6,7). Involution is accompanied by gradual changes in thymocyte populations relative to

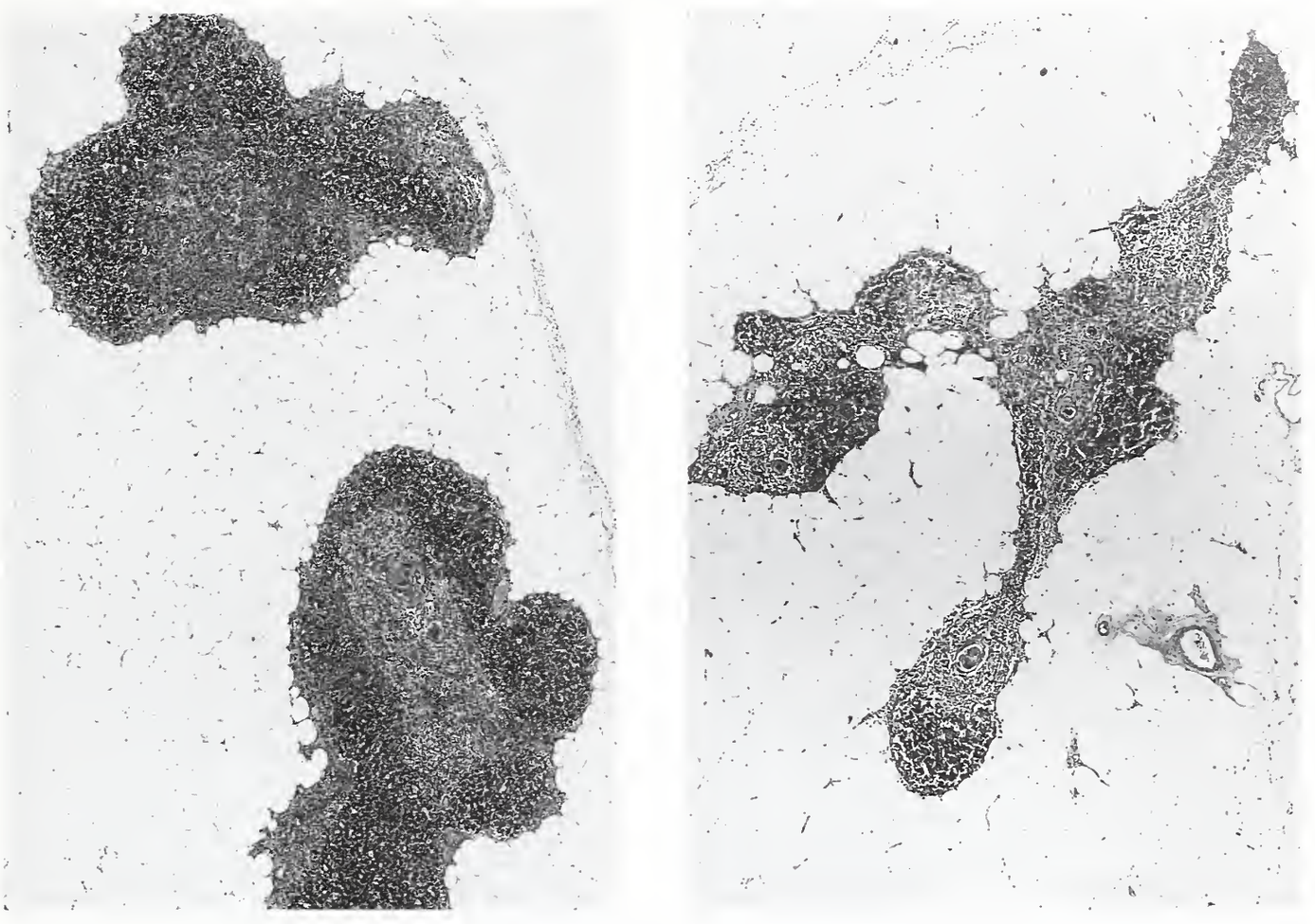


Figure 1-20
INVOLUTING THYMUS
This adult thymus shows involution with fat replacement in a 56-year-old female (left) and a 48-year-old male (right).

different rates of involution of the cortical and medullary epithelium and a decline in the production of thymic hormones by thymic epithelial cells. However, the thymus continues to serve as the site of T-cell differentiation and maturation throughout life. In the young adult, the parenchymal loss is primarily due to a decreasing number of cortical thymocytes, with relative sparing of the epithelial elements. With advancing age, the epithelial component atrophies, and the gland consists of islands of spindle-shaped epithelial cells, with partially cystic, closely arranged Hassall corpuscles and scattered small lymphocytes in abundant adipose tissue (fig. 1-20). This gradual decrease in the volume of the thymus is followed by a more gradual decrease in the volume of the peripheral T-lymphocyte compartment. The most striking microscopic changes seen in connection with involution relate to the distribution, architectural arrangement, and cytologic appearance of the epithelial cells (fig. 1-21) (7). Some of the epithelial cells have a spindle, mesenchymal-like appearance, while others arrange themselves in rosette-like formations devoid of central lumina. Sometimes, the thymic remnant may be mistaken for a neoplastic process due to the formation of round, solid epithelial nests or elongated strands of epithelial cells. These architectural formations may present within lymphoma or seminoma and may be misinterpreted as evidence of the epithelial nature of the neoplasm (7).

Thymic remnants are often made up almost exclusively of lymphocytes, thus simulating lymph nodes (7). The involuted lymphoid tissue of the thymic remnant in fatty tissue, unlike the ordinary lymph node, does not have a capsule. In addition, with careful search of the periphery of the nest,

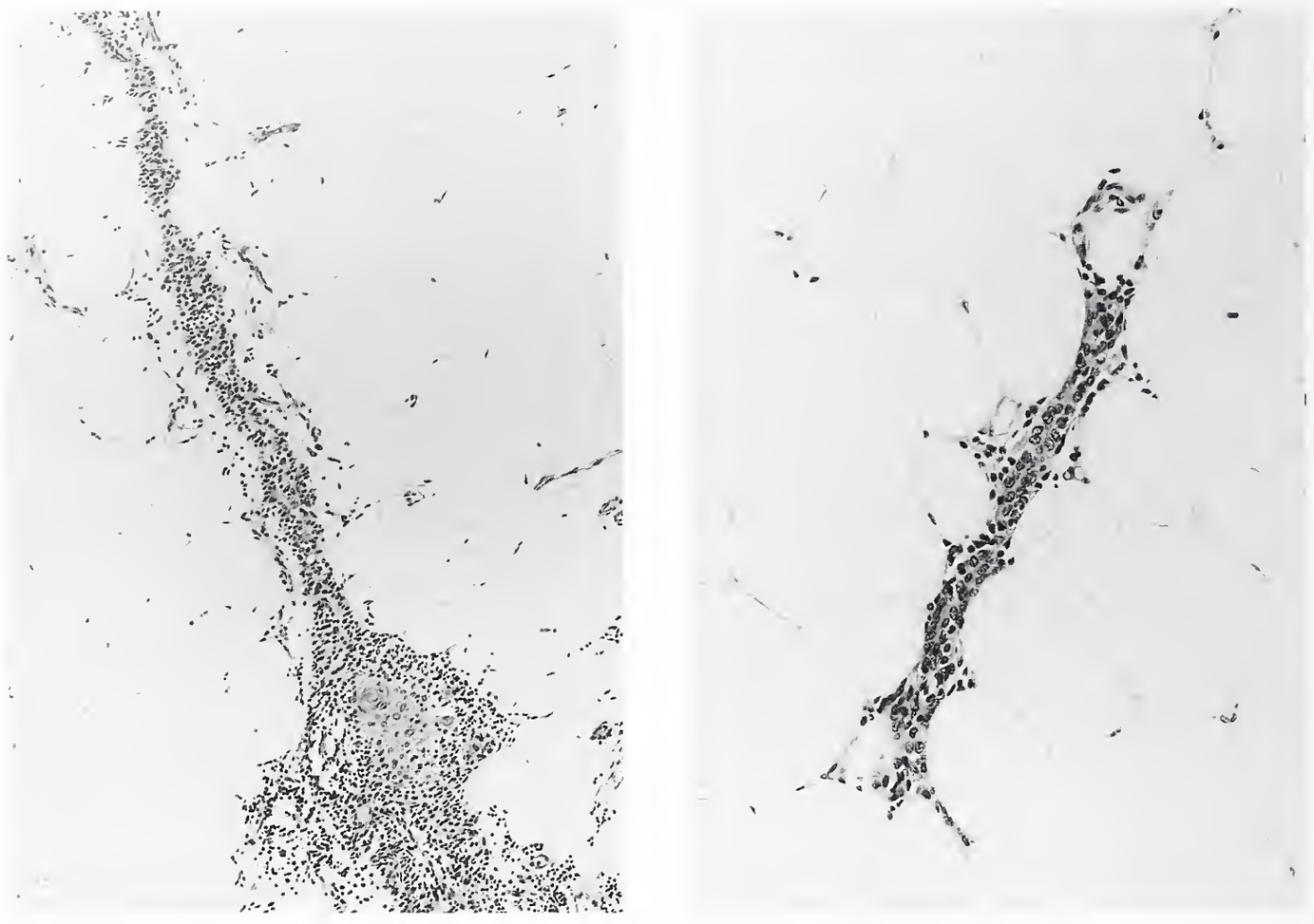


Figure 1-21
INVOLUTED THYMUS OF A 71-YEAR-OLD MALE
Left: Abortive Hassall corpuscles are surrounded by small lymphocytes and inconspicuous epithelial cells.
Right: Strands of epithelial cells surrounded by a few small lymphocytes are seen within the fat.

one may find epithelial cells encircling the nests, representing the residual coat of subcapsular cortical cells of the normal organ. Although the thymus in elderly individuals may look totally replaced by adipose tissue, microscopic thymic remnants are almost always recognizable.

By active lymphopoiesis the thymus responds dramatically to episodes of severe stress by a loss in size and weight. This accidental or stress-related involution results from a sudden release of corticosteroids from the adrenal cortex which causes rapid lympholysis of the cortical thymocytes. There is a prominent karyorrhexis of thymocytes and active phagocytosis by macrophages, which create a prominent starry sky appearance characteristically confined to the cortex (fig. 1-22) (7,18). Continuing stress results in extensive lympholysis with a loss of corticomedullary distinction and an accentuation of the epithelial cells, cystic dilatation of Hassall corpuscles, and elongation of epithelial cystic spaces (fig. 1-23). With further loss of thymocytes, the lobular architecture progressively collapses and fibrosis ensues. Clinically significant immunosuppression due to extensive loss of cortical thymocytes may be seen in children undergoing major stress, such as with extensive thermal injury. Radiotherapy and intensive antitumor chemotherapy induce morphologic changes similar to those of stress involution (fig. 1-24) (7).

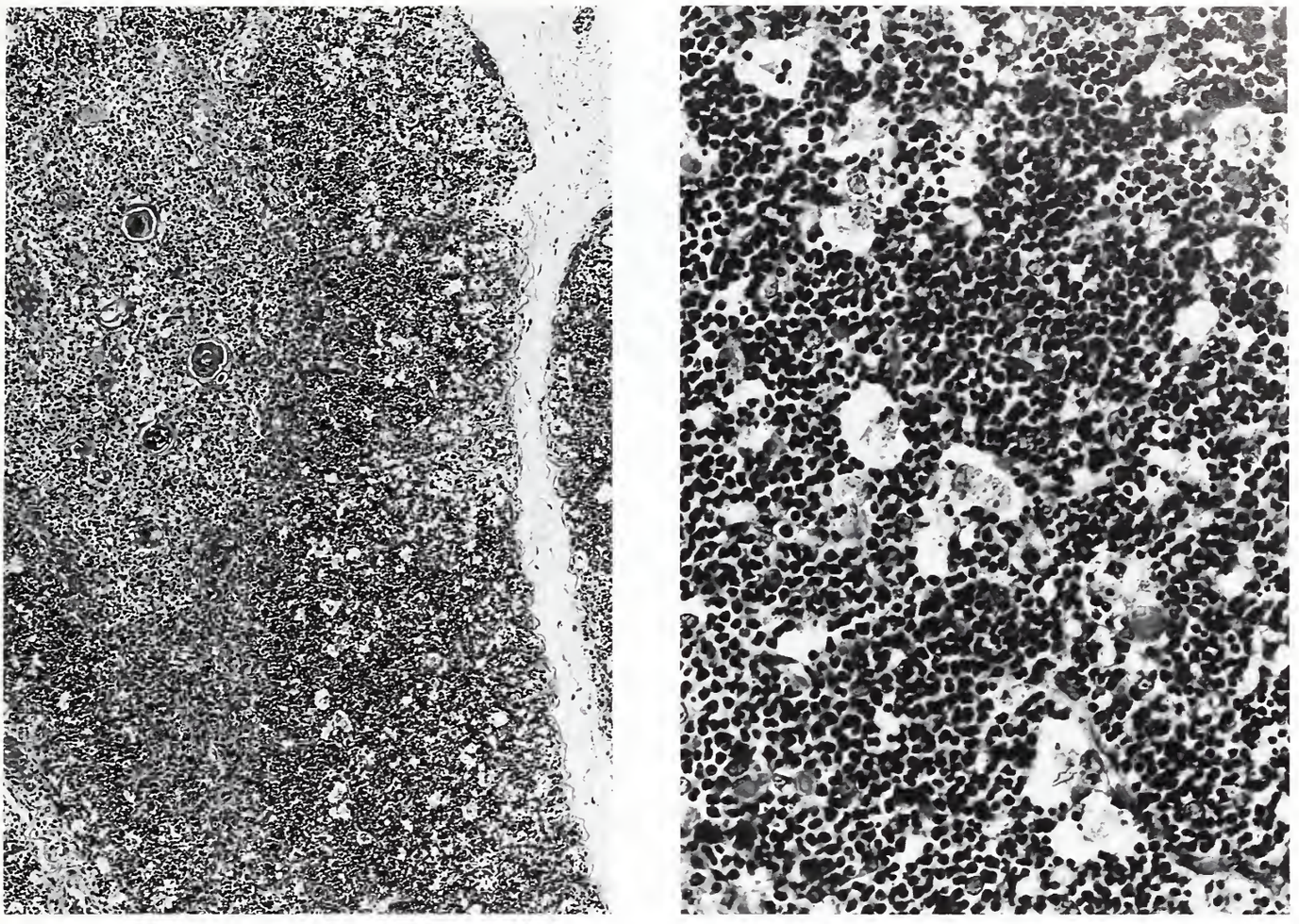


Figure 1-22
ACUTE THYMIC INVOLUTION WITH "STARRY SKY" APPEARANCE IN THE CORTEX OF AN INFANT
An abundance of macrophages containing degenerating lymphocytes and nuclear debris in the cortex of the thymus is shown. (Left: low-power view; right: high-power view.) (Courtesy of Dr. Junichi Hata, Tokyo.)

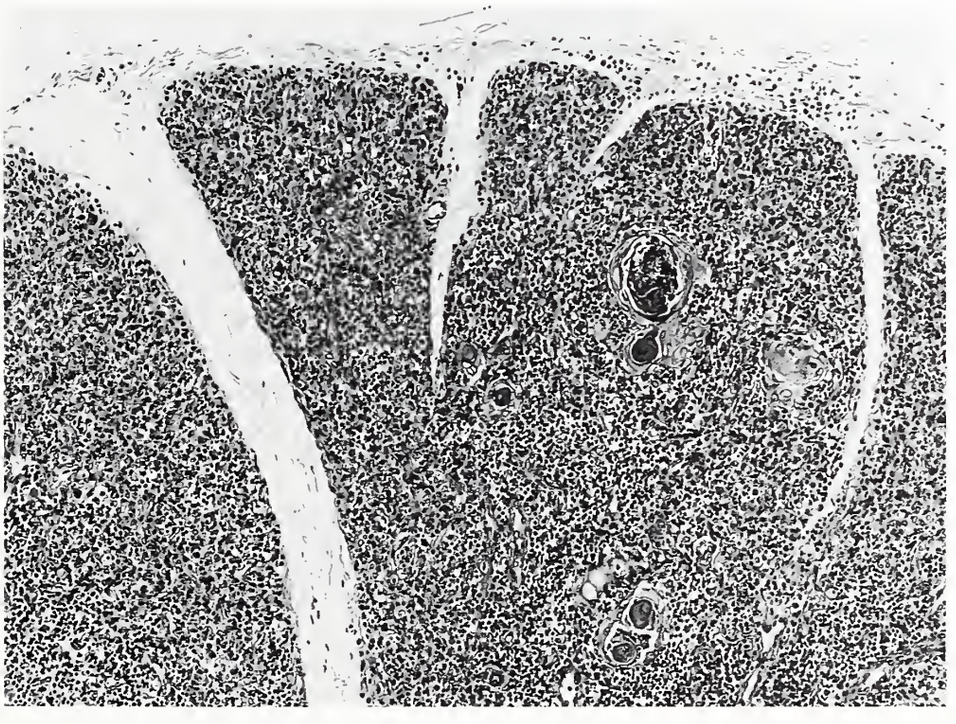


Figure 1-23
CHRONIC THYMIC INVOLUTION IN A 6-MONTH-OLD FEMALE WITH EBSTEIN'S ANOMALY
The thymus weighed 3 g. Lobulation is distinct. Loss of cortico-medullary demarcation and marked reduction in the number of lymphocytes are the prominent features. (Courtesy of Dr. Junichi Hata, Tokyo.)

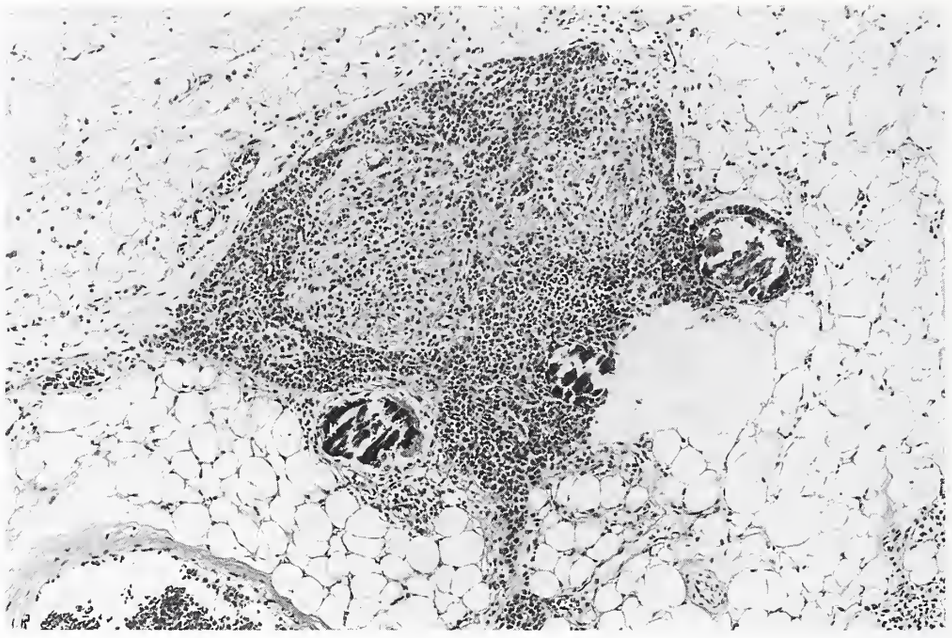


Figure 1-24
INVOLUTED THYMUS IN A CASE OF MEDIASTINAL CHORIOCARCINOMA TREATED BY CHEMOTHERAPY

Thymus lobule is reduced in size showing marked reduction in the number of lymphocytes as well as fibrosis. Calcified Hassall corpuscles are surrounded by nests of epithelial cells.

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2
NON-NEOPLASTIC CONDITIONS OF THE THYMUS

THYMUS IN IMMUNODEFICIENCY

Since the thymus is an important organ in the development and maintenance of the immune system, it is not surprising to find that morphologic changes in this organ are associated with various immunodeficiency disorders (2,3,6). The thymus is unique in several aspects when compared with other lymphoid organs; these characteristics also contribute to the distinct histologic changes associated with immunodeficiency disorders.

The morphologic changes are divided into congenital (thymic dysplasia) and acquired (thymic atrophy) (Table 2-1) (6). Morphologically, the dysplastic thymus shows depletion of lymphoid cells and lack of maturation of the epithelial cells, which appear primitive and fail to differentiate into Hassall corpuscles (fig. 2-1). Thymic dysplasia is present at birth and is thought to express a failure or arrest in the embryologic development of the organ. The terms "thymic hypoplasia" and "thymic alymphoplasia" are outdated designations and should be regarded as equivalent to, or variants of, dysplasia. The term "thymic aplasia" as observed in Di George's syndrome should be restricted to those cases with complete absence of a eutopic thymus gland, possibly with tiny remnants of normal mature tissue.

By contrast, thymic atrophy designates all regressive changes that are postnatally acquired and is characterized by shrinkage of the thymus, depletion of the lymphoid population, and a varying degree of alterations in the epithelial network (see figs. 1-23, 1-24) (6). The World Health Organization (WHO) divides human immunodeficiencies into primary (mostly inherited) and secondary acquired states (2). This

Table 2-1

A COMPARISON OF THE FEATURES OF INHERITED THYMIC DYSPLASIA (ITD) AND SEVERE THYMIC ATROPHY (STA)*

	ITD	STA
Weight of the gland	< 5 g	> 5 g
Foliated architecture	Well preserved	Blurred
Interlobular and perilobular tissue	Fatty	Fibroadipose with inflammatory cells
Size of the vessels	Small	Enlarged for the size of the lobules
Perivascular spaces	Empty	Fibrohyaline deposits
Thymic epithelial network	Maintained	Collapsed and disorganized
Epithelial maturation	Totally defective	Partially defective
Hassall corpuscles	Absent	Absent or necrotic and calcified
Cytokeratin expression	Present	Often reduced
Class II MHC expression	Present	Present
Lymphoid cells		
CD1	Absent	Absent
CD2	Absent or rare	Some present
CD4	Absent	Some present
CD8	Absent	Some present
Plasma cells	Absent	Present, sometimes numerous

*Table 1 from Nezelof C. Thymic pathology in primary and secondary immunodeficiencies. Histopathology 1992;21:499–511.

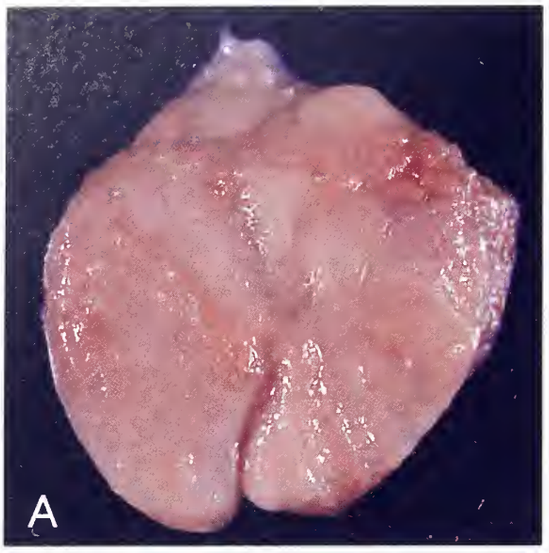
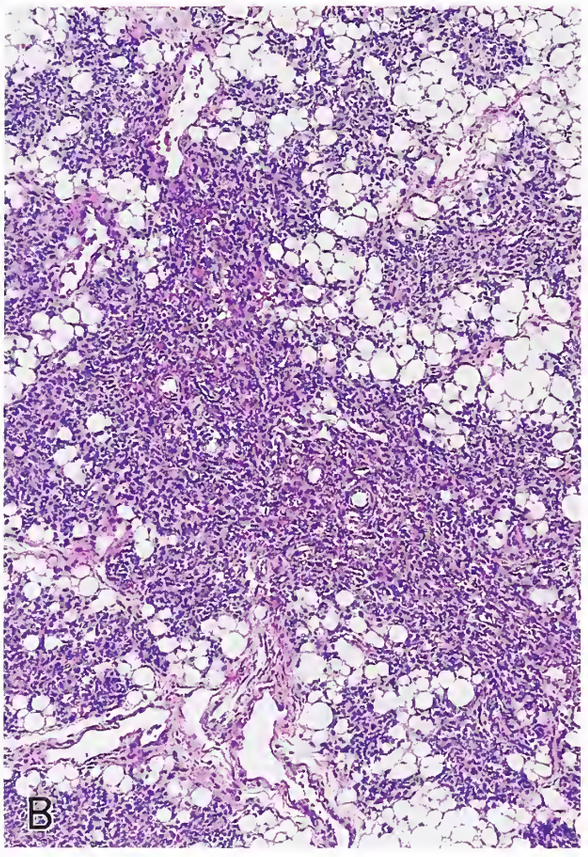


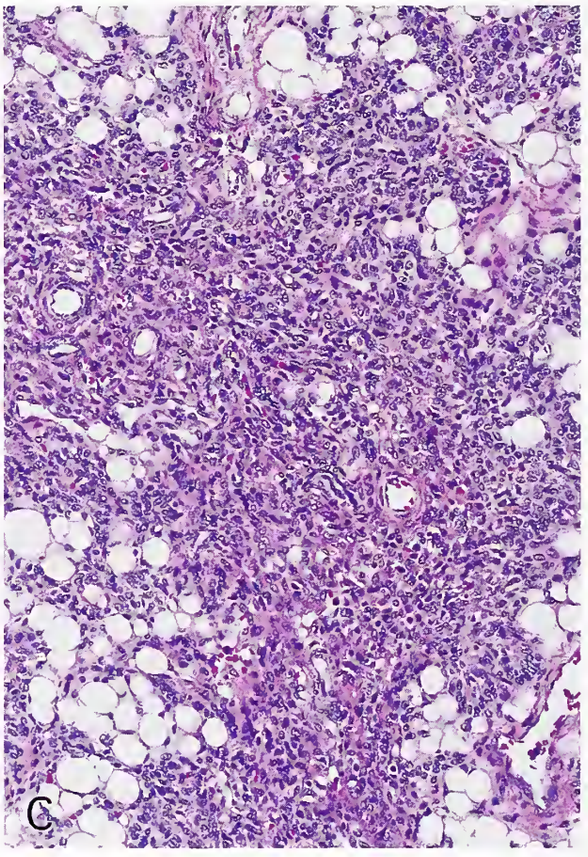
Figure 2-1
THYMIC DYSPLASIA IN A 2-MONTH-OLD MALE WITH ADENOSINE DEAMINASE–DEFICIENT SEVERE COMBINED IMMUNODEFICIENCY

A: The thymus weighed only 0.8 g and consisted of loose fibrotic tissue with scattered fat lobules.

B: Low-power photograph reveals a vaguely foliated architecture with irregular borders of the thymic parenchyma.

C: Higher power view discloses absence of Hassall corpuscles, aggregates of spindle-shaped epithelial cells, rare lymphoid cells, and scattered fat cells. (Courtesy of Dr. Junichi Hata, Tokyo.)





provides a convenient way to study separately the inherited disorders, represented mainly by the dysplastic lesions, and the acquired conditions, characterized by atrophic changes (Table 2-2).

Thymus in Primary Immunodeficiencies

The primary immunodeficiency disorders are a heterogeneous group of genetic or acquired cellular defects that result in the faulty maturation, regulation, or function of antigen-specific lymphocytes (8). Several classifications of immunodeficiency have been proposed, but none is fully satisfactory. One of the current classifications of these disorders is based on criteria that define altered functions of B or T lymphocytes or both (8). As a group, these disorders are rarely encountered in clinical medicine, their frequency being less than 1 case per 50,000 to 100,000 population (3).

Table 2-2

MAJOR IMMUNODEFICIENCY DISORDERS ASSOCIATED WITH AN ABNORMAL THYMUS GLAND*

Syndrome	Thymic Morphology	Inheritance
Congenital thymic hypoplasia (DiGeorge's syndrome)	Dysplasia	S**
Severe combined immunodeficiencies (SCID)		
Reticular dysgenesis	Dysplasia	AR**
Nezelof's syndrome	Dysplasia	XL/AR
Adenosine deaminase deficiencies	Dysplasia	AR
Purine nucleoside phosphorylase deficiency	Dysplasia	AR
Ataxia telangiectasia	Dysplasia	AR
MHC antigen deficiency†	Atrophy	AR
Wiskott-Aldrich syndrome	Atrophy	XL
Acquired immunodeficiency syndrome (AIDS)	Atrophy	S
Immunodeficiency to Epstein-Barr virus	Atrophy	XL/AR
Graft versus host disease	Atrophy	S

*Modified from Table 29-4 from Griffith RC. Thymus gland. In: Kissane JM, ed. Anderson's pathology. St. Louis: CV Mosby, 1990:1493–516.
**S: sporadic; AR: autosomal recessive; XL: X-linked recessive.
†MHC: major histocompatibility complex.

Dysplasia of the thymus is the most frequently and thoroughly described histologic lesion of the thymus associated with primary immunodeficiency disorders. Nezelof et al. (6) described four subtypes of thymic dysplasia: simple thymic dysplasia, pseudoglandular thymic dysplasia, thymic dysplasia with cortico-medullary differentiation, and thymic pseudoatrophy. In all subtypes, the thymus shows the following common features: loss of lymphoid cells, lack of a distinct cortico-medullary junction, and lobular structures with an embryonal appearance (fig. 2-1). Pseudoglandular dysplasia is the most primitive form, whereas thymic dysplasia with cortico-medullary differentiation and thymic pseudoatrophy are the better differentiated forms.

These histologic patterns do not necessarily correlate with a precise inherited disease or a specific enzyme deficiency. They seem instead to reflect the severity of the disorder (6). While the pseudoglandular pattern, the most primitive, is usually associated with complete agammaglobulinemia, early death, and frequently a total absence of peripheral lymph nodes, the pseudoatrophic pattern correlates with normal or low levels of serum immunoglobulins, prolonged survival, and occasionally adenosine deaminase (7) or nucleoside phosphorylase enzymatic deficiency (fig. 2-1).

Well-established inherited T-cell deficiencies, such as the bare lymphocyte syndrome (lack of expression of major histocompatibility complex [MHC] class II), Wiscott-Aldrich disease, and a defect in the production of interleukin-2 are not associated with dysplastic thymus but with an otherwise normal atrophic gland (6).

The thymus of patients with Down's syndrome, who have a marked and definite defect in the thymus-dependent immune system, shows morphologic changes resembling involution (1), that is, a small thymus with severe lymphocyte depletion, diminution of the cortex, and loss of cortico-medullary demarcation. In addition, Hassall corpuscles are giant and cystic, with increased cellularity around them (fig. 2-2) (5). Although the distribution of epithelial cells positive for different subtypes of cytokeratins is similar to that in the thymus of normal children, the number of

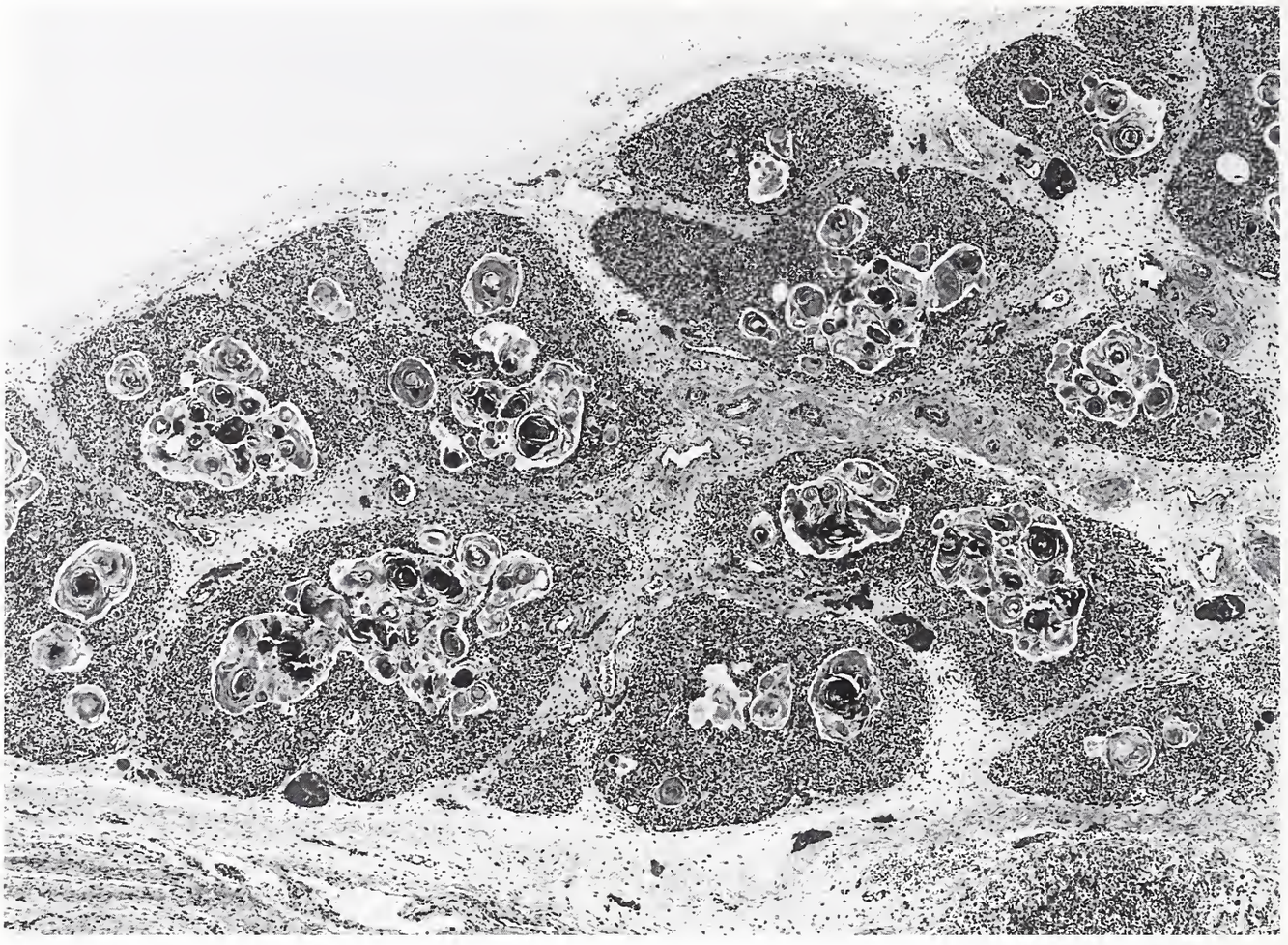


Figure 2-2
SMALL ABNORMAL THYMUS RESEMBLING INVOLUTED THYMUS
IN A 3-MONTH-OLD MALE WITH DOWN'S SYNDROME

The thymus weighed only 1 g. Lobular architecture of the thymus is maintained. Hassall corpuscles are prominent and large, probably due to coalescence. Marked diminution of the cortex with loss of cortico-medullary demarcation, marked reduction in number of lymphocytes, loss of fat cells, and fibrosis of interlobular tissue are seen.

interdigitating cells are reduced or absent (4). It is postulated that alterations in the thymic microenvironment may correlate with the imbalances of immunity in patients with Down's syndrome.

Thymus in Secondary Immunodeficiencies

Unlike inherited immunodeficiencies, acquired immunodeficiencies appear less delineated. In addition to the acquired immunodeficiency syndrome (AIDS), acquired immunodeficiency may be seen in patients with severe graft versus host disease (GVHD), chronic viral infection including late onset rubella syndrome, prolonged administration of glucocorticoid and cytotoxic drugs, severe and early protein malnutrition, and total body irradiation (figs. 1-24, 2-3) (6,9). In all these circumstances, the thymus is assumed to have been previously normal, and the morphologic changes are therefore regarded as acquired, i.e., of atrophic and degenerative nature. Nezelof uses the term severe thymic atrophy for these morphologic changes (Table 2-2).

THYMIC HYPERPLASIA

The term thymic hyperplasia embraces two distinct morphologic forms (10,13,15). The first, true thymic hyperplasia, indicates enlargement of the thymus through an increase in thymic tissue, which remains normally organized. The second form, lymphoid hyperplasia, is characterized by the presence of lymphoid follicles with germinal centers in a thymus gland that may be enlarged, atrophied, or involved by a neoplasm.

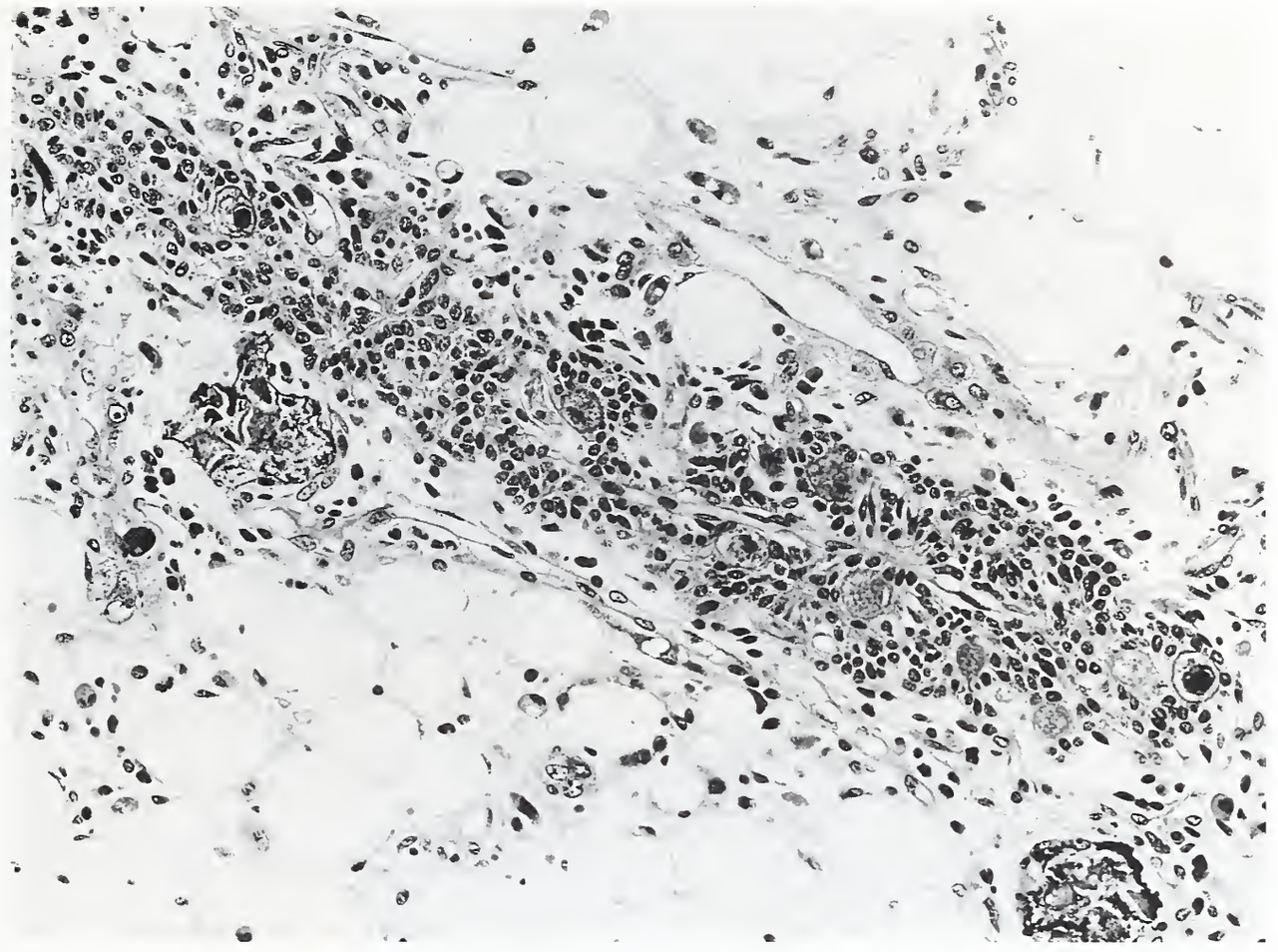


Figure 2-3
SEVERE THYMIC ATROPHY IN A 54-YEAR-OLD MALE WITH HEMOPHILIA A AND AIDS
The thymic lobule is greatly reduced in size with marked reduction in number of lymphocytes. There are several cells with cytomegalovirus inclusion bodies. A calcified Hassall corpuscle is seen in the right lower corner. (Courtesy of Dr. Morio Koike, Tokyo.)

True Thymic Hyperplasia

True thymic hyperplasia is defined as enlargement of the thymus gland (as determined by weight and volume) beyond the upper limit of normal for that particular age (figs. 2-4, 2-5). A histologically normal thymus can weigh in excess of 200 g (10). In order to establish the diagnosis of true thymic hyperplasia, reference must be made to standard weight charts of the normal thymus for comparison. The first extensive studies on the normal weights of the thymus were made in fresh autopsy specimens by Hammar in 1906 (13). These figures have recently been updated, most comprehensively by Steinmann (14) who studied the weight and volume of human thymuses in 136 healthy individuals (Table 2-3). Whether there is any ethnic or geographic difference in thymic weight is not known, and therefore using data from a single study may be misleading. The pathogenesis and significance of true thymic hyperplasia are unknown.

Thymic hyperplasia has been recognized in several instances as a complication of chemotherapy for Hodgkin's disease and germ cell tumors, and has been interpreted as the expression of an immunologic "rebound" phenomenon (figs. 2-4, 2-5) (15). A similar enlargement of the thymus has been reported in children recovering from thermal burns and in infants following cessation of administration of corticosteroids. A case of pure red cell aplasia associated with true thymic hyperplasia was reported in a 35-year-old female (12). The thymus was found to be enlarged not on chest X-ray examination but on computed tomography (CT). Thymectomy for the enlarged thymus was performed and followed rapidly by a full hematologic recovery.

Table 2-3

WEIGHT AND VOLUME OF NORMAL HUMAN THYMUSES*

Age (years)	Number	Weight (g)		Volume (cm^3)	
		$\bar{x}$	SD	$\bar{x}$	SD
0–1	6	27.3	16.4	26.8	16.1
1–4	4	28.0	19.3	27.9	10.4
5–9	7	22.1	9.2	21.5	8.8
10–14	5	21.5	6.1	21.1	6.4
15–19	9	20.2	10.3	19.3	10.1
20–24	18	21.6	9.5	23.0	10.6
25–29	9	23.1	11.8	23.7	11.9
30–34	5	25.5	9.9	27.6	11.2
35–44	17	21.9	9.2	22.2	10.5
45–54	14	24.8	12.8	26.5	12.4
55–64	15	21.3	9.5	23.5	10.4
65–84	17	23.8	16.1	25.6	17.0
85–90	5	18.2	5.4	20.4	6.8
91–107	5	12.4	6.9	13.4	7.2
	136	22.8	12.5	23.4	11.9

*Table 2 from Suster S, Rosai J. Thymus. In: Sternberg SS, ed. Histology for pathologists. New York: Raven Press, 1992:261–77.

Figure 2-4
HYPERPLASTIC THYMUS

This thymus was excised from a 5-year-old male and weighed 75 g. "An anterior mediastinal tumor," which proved to be hyperplastic thymus, was detected 2 years 3 months after resection of a testicular germ cell tumor and postoperative chemotherapy. Normal configuration of the thymus is preserved. Note the prominent lobulation on the incisional surface made at the time of sampling. (Figures 2-4 and 2-5 are from the same case.)

Lymphoid Hyperplasia

In contrast to true thymic hyperplasia, lymphoid hyperplasia of the thymus is usually not associated with enlargement of the thymus but refers to the presence of an increased number of lymphoid follicles (figs. 2-6, 2-7) (10,13,15). Since lymphoid follicles are a normal constituent of the thymus, it is difficult to establish diagnostic criteria for lymphoid hyperplasia. Lymphoid follicles arise at the cortico-medullary junction within the extrathymic perivascular spaces and are structurally similar to those of peripheral lymphoid tissues (15).

Lymphoid hyperplasia of the thymus is most commonly associated with myasthenia gravis but has also been observed in a number of immunologically mediated disorders including systemic lupus erythematosus, rheumatoid arthritis, scleroderma, allergic vasculitis, and thyrotoxicosis (10,13,15). The pathogenesis of myasthenia gravis has been a topic of interesting but controversial debates (16). Discovery of circulating antibody against postsynaptic acetylcholine receptor (AChR) has lead to an extensive study of the

Figure 2-5
HYPERPLASTIC THYMUS
Thymic cortices and medullae are well defined. Interstitial connective tissue is delicate with rare fat cells. There is no germinal center.

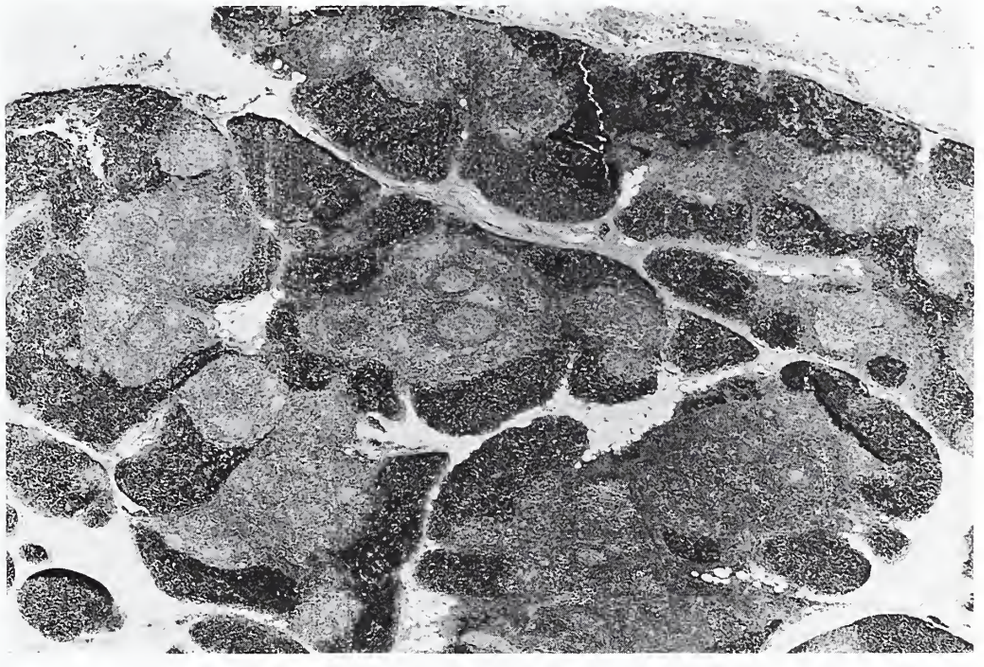


Figure 2-6
LYMPHOID HYPERPLASIA OF THYMUS IN A 21-YEAR-OLD FEMALE WITH MYASTHENIA GRAVIS
A low-power photomicrograph shows the absence of involution, many lymphoid follicles with germinal centers in the medulla, and moderate compression of the cortex. (Courtesy of Dr. Kenichi Tamaoki, Isehara, Japan.)

thymic microenvironment responsible for the production of anti-AChR antibody. Immunocytochemical evaluation has demonstrated that the myoid cells in myasthenic thymuses are in very close contact with antigen-presenting interdigitating cells (11). There are also a relatively large number of AChR-specific autoimmune T cells (CD4 positive, CD8 negative) in myasthenic thymuses that are capable of helping AChR-specific B cells in the lymphoid follicles to produce pathogenic autoantibodies.

We saw a variant of lymphoid hyperplasia in a patient with thymic enlargement showing lymphoid hyperplasia and features of Castleman's disease. The patient was a 53-year-old female who had myasthenia gravis for 23 years. Symptoms progressed in spite of medical treatment, and the patient was found to have a soft tissue density in the anterosuperior mediastinum on chest roentgenogram and CT scan, which obscured the aortic arch. Diagnosis was invasive thymoma of stage II, and the patient underwent

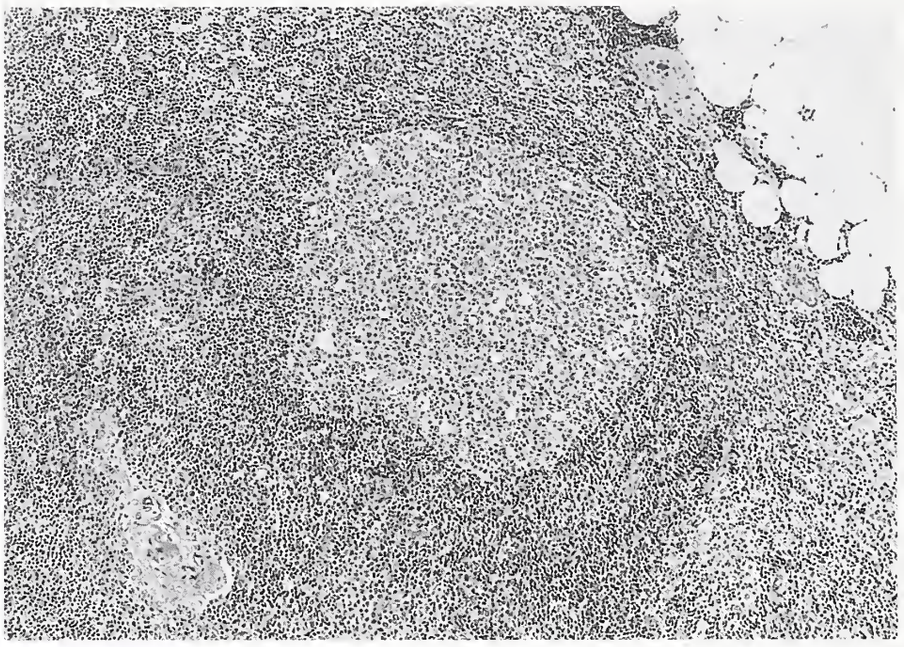


Figure 2-7
LYMPHOID HYPERPLASIA
OF THYMUS

A characteristic germinal center with a cuff of small lymphocytes in a patient without myasthenia gravis is shown.

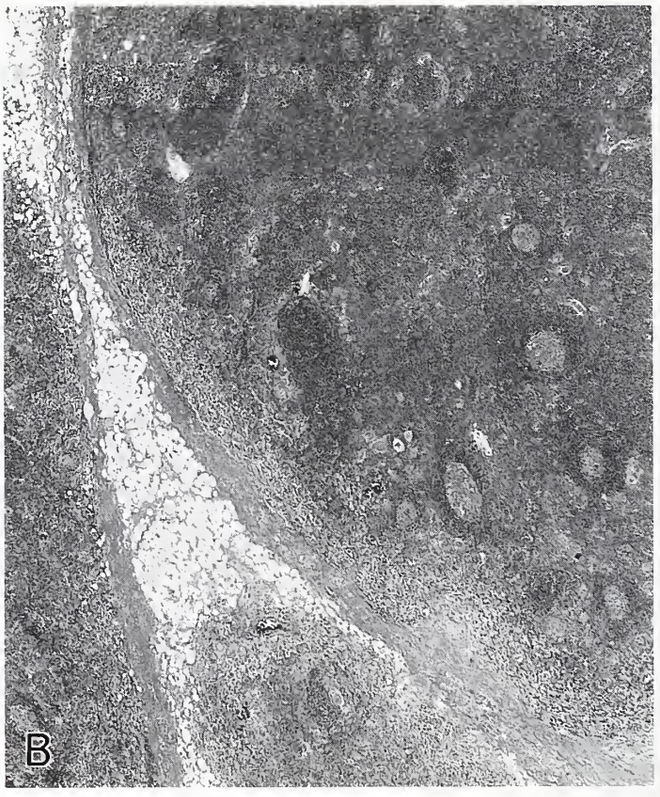


Figure 2-8
LYMPHOID HYPERPLASIA WITH FEATURES OF CASTLEMAN'S DISEASE IN MYASTHENIC PATIENT

A: Grossly the thymus is irregular and diffusely enlarged but retained the original shape of the thymus.
B: Low magnification reveals partly encapsulated thymic lobules with frequent lymph follicles having germinal centers.

total thymectomy. Grossly, the thymus showed diffuse enlargement, retaining the shape of the thymus (fig. 2-8A). Histologically, abnormal lymph follicles with germinal centers were frequent as were Hassall corpuscles and aggregates of hyperplastic small thymic epithelial cells. Germinal centers contained a few small blood vessels entering from perifollicular tissue rich in vascularity and were surrounded by concentrically arranged small lymphocytes (fig. 2-8B–D).

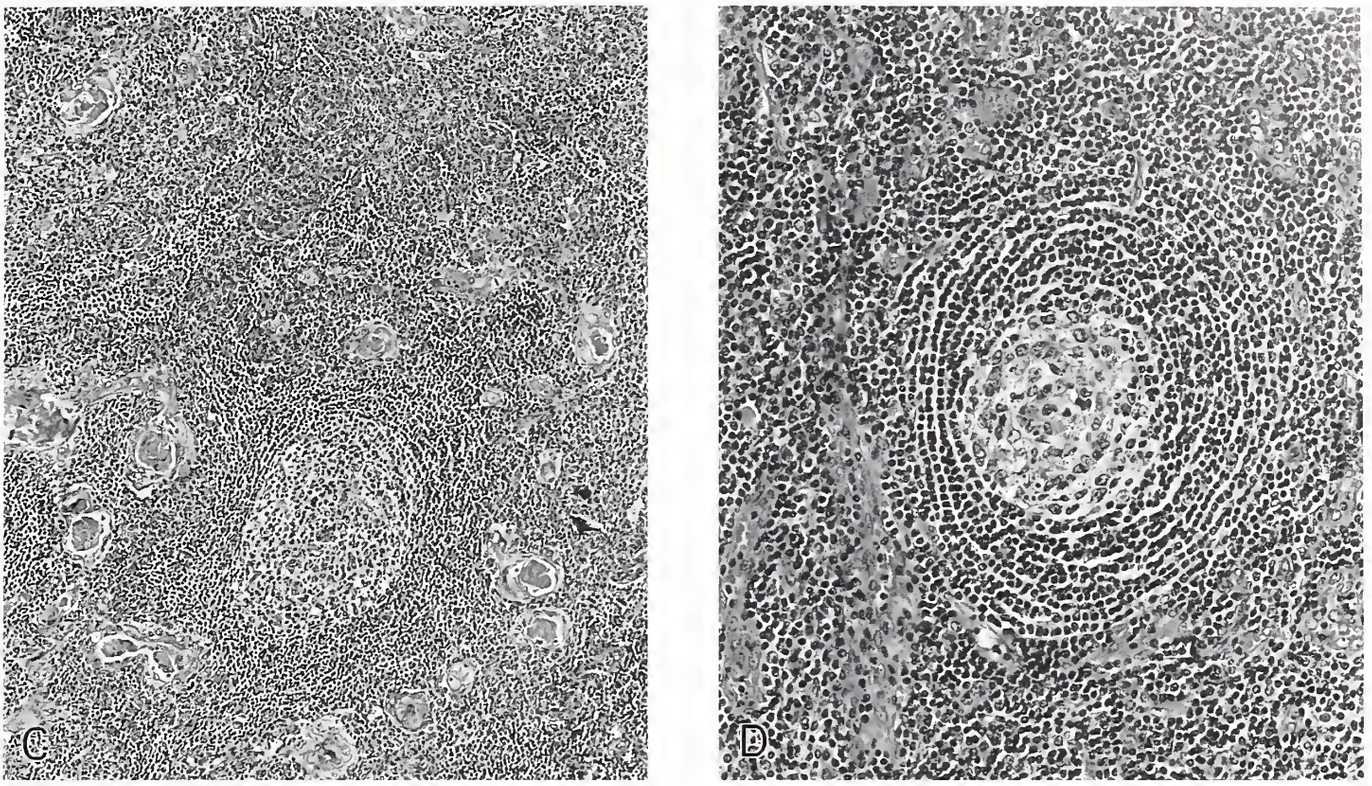


Figure 2-8 (Continued)

C: A single lymph follicle with germinal center containing a few small blood vessels, many Hassall corpuscles, and nests of hyperplastic thymic epithelial cells is seen.

D: Small lymphocytes are concentrically arranged around the germinal center and the perifollicular tissue is very vascular. (Courtesy of Dr. Morio Koike, Tokyo, Japan.)

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3
TUMORS OF THE THYMUS AND RELATED LESIONS

CLASSIFICATION

Tumors of the thymus include thymoma, thymolipoma, carcinoid tumors, germ cell tumors, malignant lymphoma, and secondary involvement of the thymus by carcinoma (7). In the second series Fascicle on thymic tumors, published in 1976, Rosai and Levine analyzed and summarized the classifications of thymic tumors proposed by various investigators up to 1968, and pointed out the presence of "inconsistencies, inaccuracy, and in some instances, mistaken concepts" (Table 3-1).

Since then, a few more classification schemes have been proposed, mainly representing modifications of those presented in the previous Fascicle. These schemes are summarized in Table 3-2 (2,3,9–12). Modifications have resulted from recognition of new entities, such as diffuse large cell lymphoma of B-cell type with sclerosis, and a variety of thymic carcinomas (5,10–12). In addition, a histogenetic classification of thymic epithelial tumors has been proposed, using an approach quite different from that of the current classification schemes (1,4,6).

Despite this cumulative work, there is still controversy regarding the classification of thymoma, thymic carcinoma, and carcinoid tumor (8). This is understandable because the origin of certain tumors and their interrelationships are not fully clarified. In this Fascicle we use the classification that is most widely used at present, since it is easily understandable and readily applicable. The classification schemes of Lewis et al. (3) and Rosai and Levine (2,7), are slightly modified. In their schemes, factors considered for the morphologic typing of thymic tumors were epithelial cell morphology and the functional aspects of the epithelial cells such as maturation of T cells, association of myasthenia gravis, and disease outcome. Although thymoma presents a variety of histologic features, no more detailed subtyping was attempted, except for listing by the predominant cell component, i.e., epithelial, lymphocytic, or mixed, and by the epithelial cell type, i.e., polygonal or spindle cell type, with or without cell atypia. Thymomas presenting a special morphology were described separately. In contrast, thymic carcinoma has been divided into several subtypes recently. The validity of such subtyping should be reevaluated.

THYMOLIPOMA AND HAMARTOMATOUS LESIONS

Thymolipoma

Thymolipoma should be distinguished from lipoma and lymphoid hyperplasia. Lipoma is one of the most common benign mesenchymal tumors of the mediastinum. It is often as large as thymolipoma. It can be located anywhere in the mediastinum and is made up of mature fat cells. Thymolipoma (or *lipothymoma*) often presents as a large asymptomatic mass in the anterior mediastinum. It can occur in both sexes at any age, but the mean age of patients is relatively young (20 to 30 years). It is a rare tumor, accounting for 2 to 9 percent of all thymic tumors. Most tumors weigh over 500 g and often exceed 2,000 g (range, 10 to 6,000 g). Patients may complain of symptoms attributable to the tumor mass, such as respiratory or cardiac difficulty (24).

Grossly, the tumor diffusely enlarges the thymus, which often retains its normal configuration. The cut surface is yellow and is lobulated due to fibrous strands, resembling lipoma (figs. 3-1A, 3-2). However, a close look discloses milky white streaks and small nodules of thymic tissue (25).

Histologically, thymolipoma is composed of mature fat and thymic tissue. The latter appears normal, although the medullary compartment may be reduced, with a scarcity of Hassall corpuscles (fig. 3-1B,C). A proportional increase of both thymic tissue (epithelial and lymphocytic) and mature fat indicates true hyperplasia of the thymus. However, a case we studied showed prominence of cortical epithelial cells bordering the thymic parenchyma as well as the medullary epithelium, with numerous Hassall corpuscles (fig. 3-3). These findings favor the hamartomatous nature of thymolipoma. Thymolipoma with clusters of polygonal myoid cells with eosinophilic cytoplasm in the medulla has been reported (18). The cells were positive for myoglobin and had a Z-band structure ultrastructurally.

Table 3-1

PROPOSED CLASSIFICATIONS OF THYMIC TUMORS I (up to 1968)*

Ewing (1916)
- Lymphosarcoma or thymoma
- Carcinoma (arising from the reticulum cells)
- Spindle cell sarcoma or myxosarcoma

Symmers (1932)
- Perithelioma
- Lymphosarcoma
- Epithelioma
- Spindle cell sarcoma
- Hodgkin's disease

Hellwig (1941)
- Lymphosarcoma
- Leukosarcoma
- Hodgkin's disease
- Carcinoma

Lowenhaupt (1948)
- Carcinoma of primitive epithelial reticulum
- Carcinoma of variegated cell pattern
- Carcinoma of granulomatous pattern
- Carcinoma of thymic round cell (lymphoepithelioma)
- Encapsulated thymoma (lymphosarcoma)
- Carcinoma of adamantinomatous pattern

Effler and McCormack (1956)
- Lymphomatous
  - Lymphocytic
  - Hodgkin's disease
- Carcinomatous
  - Lymphoepithelioma
  - Epithelial

Thomson and Thackray (1957)
- Epithelial
  - Differentiated or epidermoid
  - Oval or spindle cell
  - Lymphoepithelioma
  - Granulomatous
  - Undifferentiated
- Lymphoid
- Teratomatous

Andritsakis and Sommers (1959)
- Epithelial
  - Undifferentiated
  - Reticular
    - Spindle cell
    - Clear cell
  - Trabecular
  - Epidermoid
  - Glandular
  - Adenoacanthomatous
- Lymphoid
- Embryonic
- Fatty
- Cystic
- Hyperplastic

Bernatz et al. (1961)
- Predominantly lymphocytic
- Predominantly epithelial
- Predominantly mixed
- Predominantly spindle cell

Böhm and Strauch (1962)
- Epithelioma
  - Spindle cell
  - Reticular
  - Solid to adenoid
  - Mixed
- Carcinoma

Lattes (1962)
- Predominantly lymphoid
- Predominantly spindle cell
- Predominantly epithelial
- Predominantly rosette forming (pseudorosette type)
- Atypical epithelial thymoma with granulomatous foci
- Granulomatous thymoma
- Seminoma-like tumor of the thymus

Legg and Brady (1965)
- Small cell
- Protoplasmic
- Spindle cell

Watanabe (1966)
- Lymphocytic
- Mixed
  - Even mixture
  - Predominantly lymphocytic
  - Predominantly epithelial
- Epithelial
  - Polygonal
  - Spindle

Friedman (1967)
- Lymphoepithelial
  - Thymoma
  - Lymphoepithelioma
  - Thymocarcinoma
- Teratoid
  - Germinoma
  - Teratoma
  - Teratocarcinoma
  - Embryonal and choriocarcinoma
- Lymphomas
  - Lymphosarcoma
  - Hodgkin's disease
- Myoid tumors
  - Myosarcoma

Fisher (1968)
- Lymphocytic
- Epithelial
- Mixed lymphocytic and epithelial (lymphoepithelioma)
- Granulomatous
- Seminoma-like
- Squamous cell carcinoma
- Thymolipoma

*From Table 3, Fascicle 13, 2nd Series.

Table 3-2

PROPOSED CLASSIFICATION OF THYMIC TUMORS II (1976 to present)

Rosai and Levine (1976)
- Thymoma
  - By cell type: round-oval cell
    spindle cell
    mixed
  - By degree of lymphocytic infiltration: absent, scant, moderate, predominant
  - By extent: encapsulated, invasive
- Thymolipoma
- Carcinoid tumor
- Germ cell tumors
- Malignant lymphoma
- Tumor-like conditions

Levine and Rosai (1978)
- Thymoma
  - Circumscribed
  - Malignant:
    - Type I (invasive thymoma with no or minimal atypia)
    - Type II (cytologically malignant = thymic carcinoma)
      - Squamous cell carcinoma
      - Lymphoepithelioma-like carcinoma
      - Clear cell carcinoma
      - Sarcomatoid carcinoma
      - Undifferentiated carcinoma

Wick et al. (1982) and Lewis et al. (1987)
- Composed of thymic epithelial cells
  - Thymoma (cytologically benign)
    - By extent: encapsulated
      invasive
      metastasizing
    - By cell type: predominantly lymphocytic
      mixed lymphoepithelial
      predominantly epithelial
      spindle cell
  - Thymic carcinoma (cytologically malignant)
    - Lymphoepithelioma-like poorly differentiated carcinoma
    - Spindling squamous cell carcinoma
    - Sarcomatoid carcinoma
    - Small cell neuroendocrine carcinoma
- Composed of other elements
  - Thymic carcinoid and neuroendocrine tumors
  - Germ cell tumors
  - Malignant lymphomas
  - Thymolipoma and thymoliposarcoma

Snover et al. (1982)
- Thymic carcinoma
  - Squamous cell carcinoma
  - Lymphoepithelioma-like carcinoma
  - Undifferentiated carcinoma
  - Small cell undifferentiated (oat cell) carcinoma
  - Mixed small cell undifferentiated squamous cell carcinoma
  - Basaloid carcinoma
  - Mucoepidermoid carcinoma
  - Clear cell carcinoma
  - Sarcomatoid carcinoma

Suster and Rosai (1991)
- Thymic carcinoma
  - Low-grade histology
    - Well-differentiated (keratinizing) squamous cell carcinoma
    - Well-differentiated mucoepidermoid carcinoma
    - Basaloid carcinoma
  - High-grade histology
    - Lymphoepithelioma-like carcinoma
    - Small cell/neuroendocrine carcinoma
    - Undifferentiated/anaplastic carcinoma
    - Sarcomatoid carcinoma
    - Clear cell carcinoma

Müller-Hermelink et al. (1985, 1992)
- Thymoma
  - Medullary
  - Mixed (medullary and cortical)
  - Predominantly cortical
  - Cortical
- Well-differentiated thymic carcinoma (organotypical, low grade)
- Thymic carcinoma
  - Epidermoid
  - Undifferentiated
  - Endocrine carcinoma-carcinoid
- Germ cell tumors
- Malignant lymphomas

Present Fascicle (Shimosato and Mukai)
- Thymolipoma and hamartomatous tumor
- Tumors of thymic epithelium
  - Thymoma
    - By extent:
      - circumscribed
        - encapsulated
        - nonencapsulated (invasive but confined to within thymus)
      - invasive (invading neighboring organs)
      - with implantation or metastasis
    - By histology: lymphocyte predominant
      mixed lymphocytic and epithelial
      epithelial cell predominant
    - By cell type: spindle cell
      mixed spindle cell and polygonal cell
      polygonal-oval cell
    - By cell atypia: absent, slight, moderate, and marked
  - Thymic carcinoma
    - Squamous cell carcinoma (well, moderately, and poorly differentiated)
    - Basaloid carcinoma
    - Mucoepidermoid carcinoma
    - Adenosquamous carcinoma
    - Adenocarcinoma
    - Small cell/neuroendocrine carcinoma
    - Lymphoepithelioma-like carcinoma
    - Large cell carcinoma
      - Clear cell carcinoma
    - Sarcomatoid carcinoma
- Tumors composed of other elements
  - Carcinoid tumor
  - Germ cell tumors
  - Malignant lymphomas

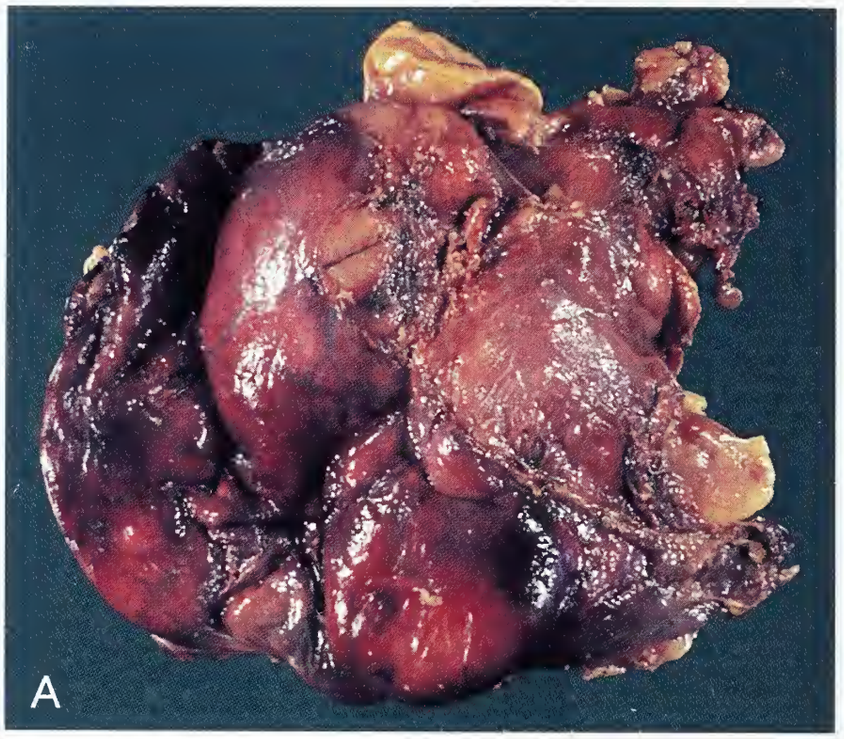
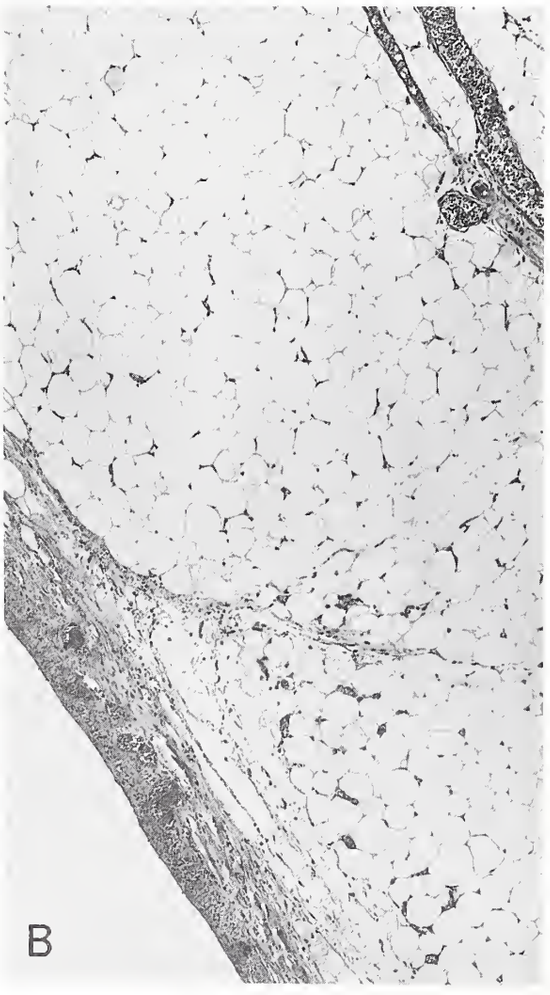


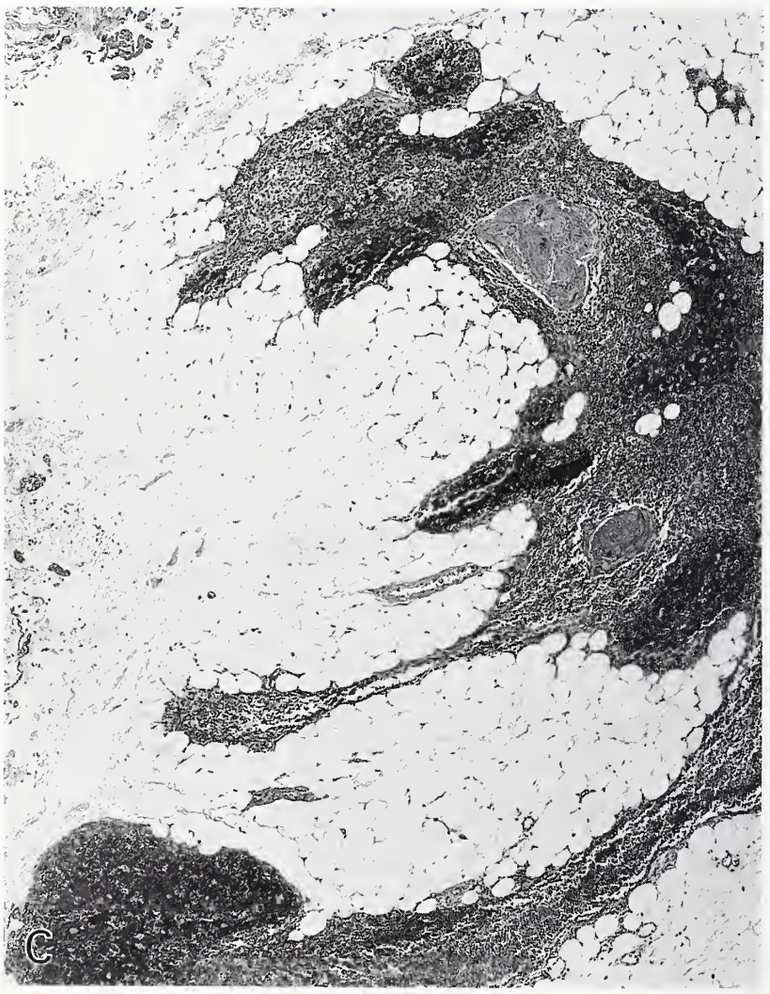
Figure 3-1
THYMOLIPOMA

A: Tumor in a 27-year-old female is large, yellowish tan, lobulated, and soft, and weighs 600 g.

B: Subcapsular portion of tumor is composed of mature fat.

C: Within fatty tissue microscopically normal thymic tissue is present. (Courtesy of Dr. Kenichi Tamaoki, Isehara, Japan.)





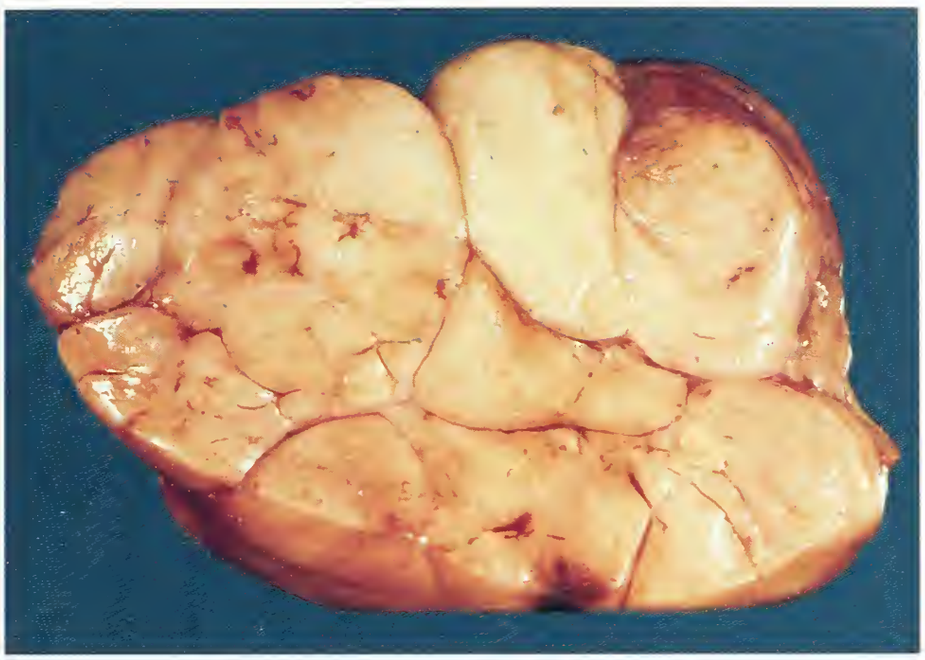


Figure 3-2
THYMOLIPOMA

The surgically resected tumor is thinly encapsulated and measures 12 x 11 x 7 cm. The cut surface is yellow, bulging, and lobulated, resembling lipoma. The patient was a 6-year-old male child. (Courtesy of Dr. Koichi Shimizu, Tokyo.) (Figures 3-2 and 3-3 are from the same case.)

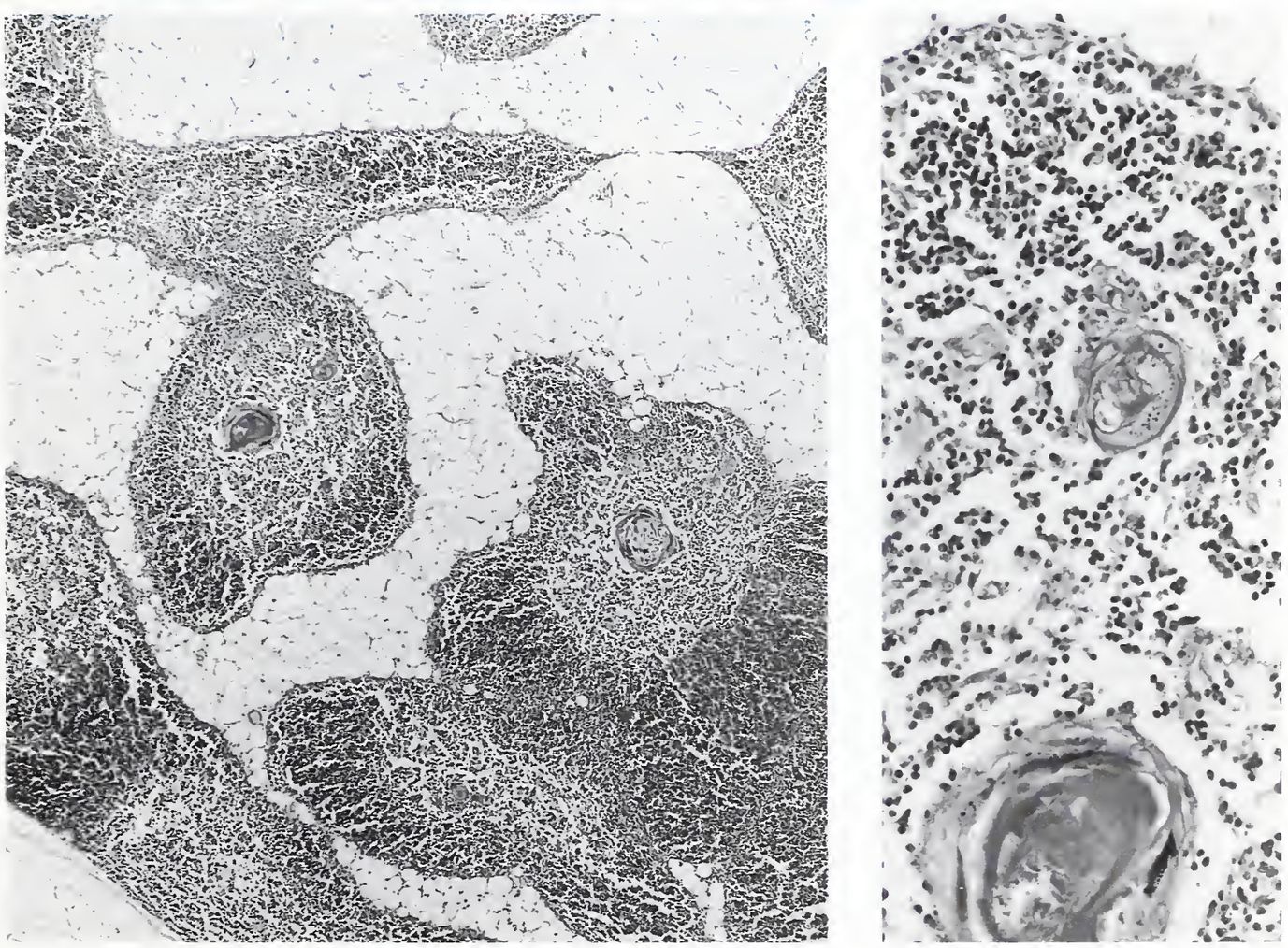


Figure 3-3
THYMOLIPOMA

Left: The tumor is composed of irregular interconnecting nests of thymic parenchyma and mature fat. The former consists of well-defined cortices and medullae with well-developed Hassall corpuscles. Note prominent cortical epithelial cells bordering the nests.

Right: Higher magnification.

Radiographically, the tumor is radiolucent. Because of this, the differential diagnosis includes cardiomegaly, pericardial cyst, and effusion. The combination of computerized tomography (CT; location and attenuation values approaching those of fat), ultrasonography (high echo due to the fat content), and magnetic resonance imaging (MRI; strong signal intensity on T1-weighted spin-echo images) should suggest thymolipoma (15,24,30).

An association with Graves' disease, Hodgkin's disease, chronic lymphoid leukemia, hypogammaglobulinemia, and aplastic anemia has been reported (13,14,22). Up to 1991, 10 cases of thymolipoma associated with myasthenia gravis had been reported (18–20,23). This association occurs more often in patients older than those presenting with thymolipoma alone; thymectomy improves the symptoms of myasthenia gravis, though they may recur postoperatively. Tumor weight is less than 200 g, with an average of 100 g, which is lower than the weight of thymolipoma unassociated with myasthenia gravis (average, 1,095 g). The presence of germinal centers has never been mentioned in either thymolipoma or the surrounding normal thymic tissue in cases complicated by myasthenia gravis. The prognosis is excellent after removal of the tumor, unless a paraneoplastic syndrome is present.

There is controversy as to the nature of thymolipoma: some consider it abnormal hyperplasia of fat tissue, others a mixed tumor of mesenchymal and entodermal origin or hamartoma, and still others a thymoma with fatty changes ("adipose involution"). Recently, Moran et al. (21) reported two cases of a histologic variant of thymolipoma, one in a 9-year-old girl and the other in a 32-year-old man, which they named "thymofibrolipoma." The tumors were composed of "extensive areas of collagenous tissue interspersed with lakes of mature fatty tissue and strands of thymic tissue or remnants of normal thymic tissue with many Hassall's corpuscles."

Ectopic Hamartomatous Thymoma

A rare benign tumor of the lower neck consisting of fat and spindle-shaped fibroblastic and epithelial cells was described at about the same time by Smith and McClure (29) and Rosai and Levine (26). This tumor was named 2 years later by Rosai et al. (27) as ectopic hamartomatous thymoma. Recently, several more cases have been reported and reviewed (16,17,28).

This entity occurs in adults of a mean age of 49.9 years, and exhibits a marked male predominance (13 to 2). The tumors are located in the supraclavicular or suprasternal region, not attached to skin or bone and are often present for many years (up to 30 years). No cases of recurrence or metastasis have been reported on follow up of 3 to 13 years (16).

Grossly, the tumor is oval and well circumscribed, varying from 12 to 19 cm in greatest dimension. The cut surface is solid, gray-white, and occasionally fasciculated. Histologically, it is well circumscribed but may merge into surrounding adipose tissue. It is composed of several elements including spindle-shaped cells, fat cells, and squamous or glandular epithelial cell nests. The most conspicuous element consists of spindle-shaped fibroblast-like cells which are arranged in interlacing bundles. A storiform pattern may be seen. The nuclei are regular, oval to elongated, and contain fine chromatin and indistinct nucleoli. Although the spindle cells appear mesenchymal in nature, cytokeratin immunostains are positive, indicating their epithelial nature (figs. 3-4, 3-5). Epithelial islands with bland nuclei are present within the spindle cell element; they take the form of solid squamous cell nests, trabeculae, anastomosing cords, tubules, glands, and cysts. Groups of fat cells are scattered, and may occupy a major portion of the tumor or be inconspicuous. Myoid cells with myoglobin resembling fetal-type skeletal muscle have also been described (28).

Histogenetically, ectopic hamartomatous thymoma is considered to arise from the thymic anlage associated with branchial pouches (17). Tumors identical to ectopic hamartomatous thymoma have not been seen in the normally located mediastinal thymus.

In 1991, Chan and Rosai (16) proposed a unifying concept for tumors of the neck showing thymic or related branchial pouch differentiation. On the benign end of the spectrum is the above described ectopic hamartomatous thymoma; in the middle of the spectrum is the ectopic cervical thymoma, which is considered to arise from cervical thymus and is histologically and biologically identical to mediastinal thymoma; and on the malignant end are spindle

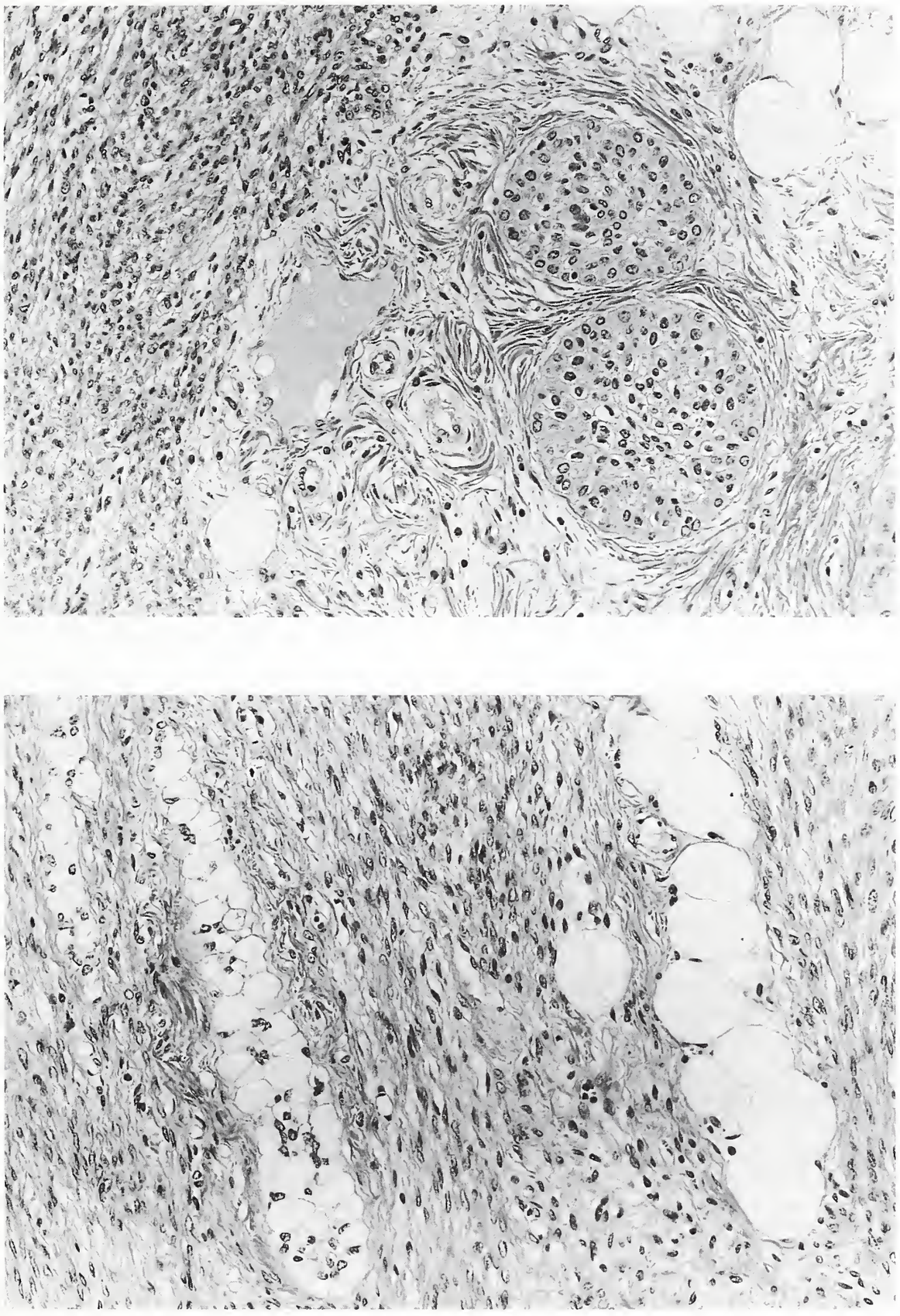


Figure 3-4
ECTOPIC HAMARTOMATOUS THYMOMA

Top: The tumor is composed of a mixture of fat cells, elongated fibroblast-like cells, and a few solid nests of squamous cells.
Bottom: Individual cells of a few epithelial nests seen in the left of the photograph are markedly vacuolated, resembling fat cells, but they are much smaller than the fat cells seen on the right. (Courtesy of Dr. Tamotsu Sugai, Morioka, Japan.)

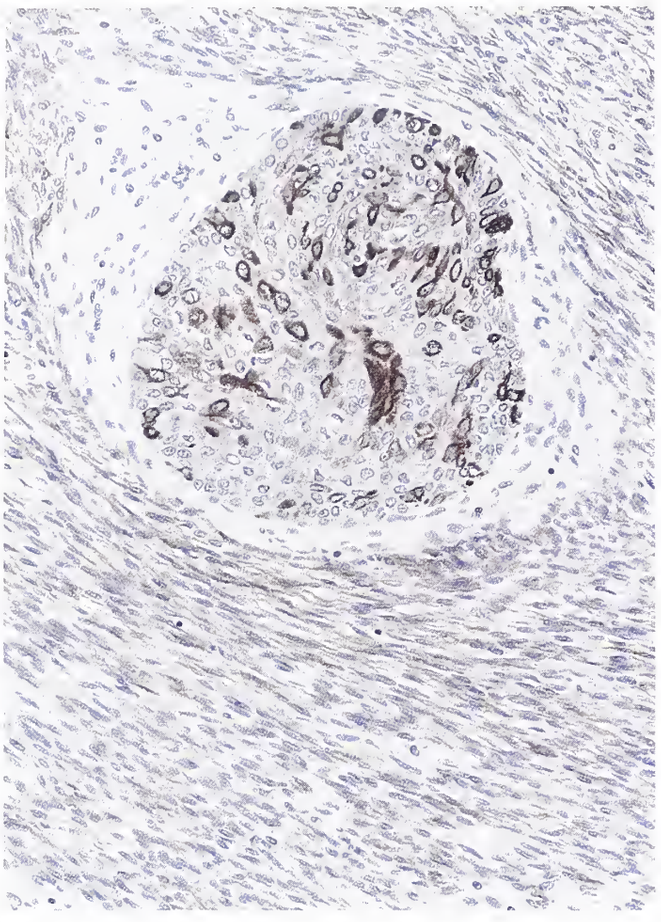


Figure 3-5
ECTOPIC HAMARTOMATOUS THYMOMA
Some squamous cells are strongly positive for cytokeratin. Fibrous tissue surrounding a squamous cell nest is negative for cytokeratin but spindle-shaped tumor cells are weakly positive. (Immunostaining for cytokeratin) (Courtesy of Dr. Tamotsu Sugai, Morioka, Japan.)

epithelial tumor with thymus-like differentiation (SETTLE) and carcinoma showing thymus-like differentiation (CASTLE). The latter resembles thymic carcinoma of lymphoepithelioma or squamous cell type.

Histologic distinction between ectopic hamartomatous thymoma and ectopic cervical thymoma is simple, since these two tumors are entirely different in nature. Characteristic findings of the former are described here and those of the latter are described with thymoma. The differential diagnosis of ectopic hamartomatous thymoma includes pleomorphic adenoma of salivary or sweat gland origin, spindle cell carcinoma, and synovial sarcoma. However, the general histologic features of relatively low cellularity, nuclear normochromasia, and absent or scanty mitotic activity enable the establishment of a correct diagnosis.

EPITHELIAL TUMORS

Thymoma

Definition. In a generic sense, thymoma means a tumor of the thymus, irrespective of cell of origin and degree of malignancy. This definition includes tumors of thymic epithelial cells, lymphocytes, fibrous tissue, vessels, fat, and any other constituents of the thymus. However, since the 1950s, thymoma was vaguely understood to be a benign or low-grade malignant tumor of thymic epithelial cell origin (37), although the concept that thymic epithelial cells and thymic lymphocytes had a common origin persisted. In the second series of this Fascicle, Rosai and Levine (92) proposed that the designation of thymoma be restricted to neoplasms of thymic epithelial cells.

Until 1976, when the second series Fascicle was published, many misnomers were used to indicate thymoma, such as mixed tumor, perithelioma, benign lymphocytic lymphoma, lymphosarcoma, reticulum cell sarcoma, and granulomatous thymoma. The reason why these terms are misnomers will be discussed in the following sections. Thymic carcinoma and lymphoepithelioma are still in use as synonyms. The former is a cytologically malignant thymic epithelial tumor (type II malignant thymoma of Levine and Rosai [66]) and the latter is designated by some pathologists as a lymphoepithelioma-like carcinoma, not a mixed lymphocytic and epithelial thymoma, very similar to undifferentiated nasopharyngeal carcinoma (undifferentiated carcinoma of the nasopharyngeal type, World Health Organization [WHO]). Many terms are used to indicate a variety of thymic carcinomas, such as basaloid carcinoma, mucoepidermoid carcinoma, clear cell carcinoma, squamous cell carcinoma, adenosquamous carcinoma, small cell neuroendocrine carcinoma, sarcomatoid carcinoma, and anaplastic carcinoma (105,107,110). These are detailed in the section dealing with thymic carcinoma.

According to the definition of Rosai and Levine (101), thymic carcinoma is included in thymoma; germ cell tumor, carcinoid tumor, and malignant lymphoma are excluded. We consider thymic carcinoma to be an entity different from the more commonly encountered "thymoma," in view of the fact that marked differences in

morphologic and functional properties exist between these two tumor types. Although described in more detail in the chapter on thymic carcinoma, we define thymic carcinoma as a tumor composed of nests and diffuse growth of obviously atypical cells of an invasive nature, as seen in carcinomas of other organs, although completely encapsulated in rare instances. There are no immature (or cortical) T cells. The phenotype of the infiltrating lymphocytes is similar to that of carcinomas of other organs (98).

Accordingly, we define thymoma as a benign or low-grade malignant tumor of the thymic epithelium with characteristic histologic features, frequently associated with a variable population of immature but non-neoplastic T cells (56,57, 98,101). Thymoma is divided into noninvasive (encapsulated or circumscribed) and invasive types; the latter occasionally shows pleural implantation and rarely lymphatic and hematogenous metastases. Cytologically, thymoma is divided into spindle cell type, polygonal (round or oval) cell type, and mixed cell type. A distinction between noninvasive, invasive, and metastasizing types on the basis of the cytologic features is impossible. In contrast, thymic carcinoma and thymoma can be distinguished histologically in most cases. The presence of immature T cells, even in implanted and distant metastatic foci of thymoma, indicates that the epithelial cells of thymoma are capable of attracting immature T cells from the bone marrow; the presence of medullary differentiation in thymoma indicates that immature T cells have the ability to mature in the environment of the thymoma. These phenomena suggest that thymoma is a functional tumor with regard to T-cell maturation. In contrast, thymic carcinoma has lost this property (98).

Müller-Hermelink and associates have recently proposed a new classification of thymic epithelial tumors based on histogenesis (52,53, 70,80). In this classification, they have separated a subtype of "well-differentiated (organotypical) thymic carcinoma of low-grade malignancy" from both thymoma and ordinary thymic carcinoma. The occurrence of such tumors has been known to pathologists, who have designated them as atypical (aggressive) thymoma, invasive thymoma with cell atypia, or a subtype of type I malignant thymoma. The term proposed by Müller-Hermelink and its relation to the thymoma subtype known as "cortical" remain controversial (58,84,100).

The lymphocytes present in thymoma are considered to be non-neoplastic, both morphologically and biologically. Although there are occasional mitotic figures, they are always present in association with epithelial components, even in implanted and distant metastatic foci. Neoplastic growth of lymphocytes occurs in the thymus as a form of Hodgkin's disease, particularly of the nodular sclerosis type; as malignant lymphoma of the lymphoblastic (T-cell) type, which becomes leukemic; as malignant lymphoma of the diffuse large cell type (B cell) with sclerosis; and rarely, as low-grade malignant MALT (mucosa-associated lymphoid tissue) lymphoma (see Malignant Lymphoma). These neoplasms are entirely different from thymoma. The only possible exception, a composite tumor containing lymphocytes and epithelial cells, was reported by Adams (31) in a 13-year-old girl who presented with acute lymphocytic leukemia and a large anterior mediastinal mass diagnosed as malignant lymphoma of the lymphoblastic type by biopsy. At autopsy, admixed with growth of lymphoma/leukemia cells, nests of atypical epithelial cells were found in the thymus and in distant metastatic foci.

Incidence. The clinical manifestations, diagnosis, pathologic features, staging, and treatment of thymoma have been reviewed recently by Morgenthaler et al. (78) who also discussed prognosis of affected patients. Thymoma is the most common and most frequently occurring neoplasm not only in the anterior mediastinal compartment but also of the entire mediastinum, if solid tumors with surgical indications are considered. There appears to be no predilection for race or sex, or geographic distribution, although females predominate over males in many published series. Table 3-3 indicates the histologic types and number of cases of mediastinal tumors resected surgically at the National Cancer Center, Tokyo, over the 30-year period of 1962 to 1992. The number of patients with thymoma initially treated at this institute, excluding those with thymic carcinoma, was 79 (31 males, 48 females); slightly more than two thymomas were resected per year. During the same period, about 2,500 lung cancers were resected. In a 45-year period (1928 to 1972) at the Memorial Sloan Kettering Cancer Center, the number of thymomas resected was 54 (34), and

Table 3-3

SURGICALLY RESECTED MEDIASTINAL TUMORS*

Histologic Types	Number	
Cyst	55	
Bronchogenic cyst		26
Thymic cyst		16
Coelomic cyst		13
Mediastinal goiter	6	
Thymic lesions	114	
Hyperplasia		8
Thymoma		79
Squamous cell carcinoma		17
Undifferentiated carcinoma		5
Carcinoid tumor		5
Germ cell tumor	60	
Teratoma, benign		45
malignant (combined malignant germ cell tumors)		12
Germinoma		1
Choriocarcinoma		2
Neurogenic tumor	67	
Paraganglioma		3
Schwannoma, benign		44
malignant		3
Neurofibromatosis		5
Ganglioneuroma		8
Neuroblastoma		2
Ganglioneuroblastoma		2
Mesenchymal tumor	6	
Lipoma		2
Liposarcoma		1
Mesenchymal chondrosarcoma		1
Malignant fibrous histiocytoma		1
Angiosarcoma		1
Malignant lymphoma**	12	
Non-Hodgkin's lymphoma+		9
Hodgkin's disease		3
Others	6	
Fat necrosis		2
Giant lymph node hyperplasia (Castleman's disease)		4
Total	326	

*National Cancer Center Hospital, 1962–1992.
**Including cases diagnosed by biopsy only.
+Including four cases of B-cell type diffuse large cell lymphoma and one case of probable low-grade B-cell lymphoma of "mucosa-associated lymphoid tissue."

in a 30-year period (1942 to 1971) at the Johns Hopkins Hospital, the number was 49 (95). Thirty-one cases were resected in 6 1/2 years between January 1978 and June 1984, according to the files of the Department of Pathology, University of Heidelberg (45), and 283 cases were resected in a 41-year period from 1941 to 1981 at the Mayo Clinic (68).

Although thymoma occurs in children, it is much more frequent in adults, particularly during the fifth and sixth decades. The median age reported is about 50 years, and in our series it was 51.8 years. Seven cases of thymoma in children under the age of 16, including four cases with "unusual features," were reported by Cajal and Suster (36), and five cases of thymoma in children aged 11 to 15 years treated at three different institutions were reported by Pescarmona et al. (85). None of the cases were associated with myasthenia gravis but one was complicated by hypoplastic anemia. Most patients had a favorable prognosis. There is one report of thymoma associated with regenerative and aplastic anemia in a 5-year-old (106). It should be noted that thymic carcinoma (type II malignant thymoma) also occurs in children, and almost always takes a rapidly aggressive course.

Clinical Findings. The majority of thymomas are found in the normal location of the thymus, i.e., the anterior mediastinum, sometimes extending to the superior compartment. Ectopic occurrence of thymoma includes the neck as high as the submandibular region and the middle or inferior mediastinum, close to either the main bronchi or diaphragm (38,68,95). Such locations result from failure of the thymus to descend or from excessive descent. The presence of thymic tissue near, or attached to, the thyroid gland is often noted in surgical specimens obtained at the time of thyroid surgery. Rarely, ectopic thymoma is present in the posterior mediastinum, the parietal or visceral pleura, or even inside the lung parenchyma (fig. 3-6) (43,49,75,77). In such cases, however, the alternative possibility of a solitary metastasis from a small undetected primary tumor in the thymus should always be considered.

The most common complication associated with thymoma is myasthenia gravis, which has been reported to occur in one third to half of all cases seen in general hospitals (68,95). Association with pure red cell aplasia or hypoplasia,

Figure 3-6
ECTOPIC THYMOMA IN THE LUNG

A 3.5 x 2.7 x 2.0 cm tumor in the posterior segment of the right upper lobe of the lung was resected by segmentectomy. The cut surface of the intrapulmonary thymoma is pale yellow and lobulated. CT of the thorax 1 year after surgery revealed neither recurrence of the tumor nor any lesion in the mediastinum. (Courtesy of Dr. Masashi Fukayama, Tokyo.)

hypogammaglobulinemia, and collagen diseases such as systemic lupus erythematosus and rheumatoid arthritis is less frequent. The frequency of thymoma complicated by such paraneoplastic syndromes was much lower in a cancer hospital, where the frequency of asymptomatic thymoma found incidentally by routine chest X-ray examination accounted for over 40 percent of all cases (34). At the National Cancer Center Hospital (Tokyo), only 11 of 79 thymomas (13.9 percent) were associated with myasthenia gravis and only 1 with pure red cell hypoplasia (56). Symptoms and signs related to the presence of thymoma include cough, chest pain, dyspnea, weight loss, unexplained fever, dysphagia, hoarseness, swollen neck lymph nodes, superior vena cava syndrome, and pleural effusion.

Diagnosis. The presence of thymoma in the anterior mediastinum is revealed by plain posterior-anterior and lateral chest roentgenograms in most instances, although tumors less than 2 cm in diameter may not be evident (44). Oval or round, often homogeneous densities with distinct borders project from the mediastinum into the right or left pleural cavity with equal frequency, and in some instances project into the bilateral pleural spaces (fig. 3-7). The tumor may have a multinodular contour.

Slightly less than half of all cases are located in the upper and middle thirds of the mediastinum and the remainder in the lower third. Calcification may be present (fig. 3-8). CT confirms the location and may reveal some characteristics of the tumor, such as cystic changes and involvement of surrounding structures such as bronchi and lung, or may reveal small tumors undetectable by plain chest X-ray examination (figs. 3-9, 3-10) (82,94). However, these findings are not specific for thymoma, and may be seen in other mediastinal tumors such as germ cell tumor, carcinoid tumor, and malignant lymphoma. Thymomas invading the lung may be difficult to differentiate from lung cancer invading the mediastinum, and thymomas located along the main bronchus may show roentgenologic features similar to those of mediastinal giant lymph node hyperplasia (Castleman's disease). However, the diagnosis of thymoma can be established almost with certainty when myasthenia gravis, red blood cell hypoplasia, or hypogammaglobulinemia is associated.

The cytologic and histologic diagnosis of thymoma can be made either by percutaneous needle biopsy or biopsy through a mediastinoscope. If a sufficient amount of material is obtained, the diagnosis is possible in most cases (figs. 3-11, 3-12). Materials obtained by aspiration for cytologic examination should be fixed immediately to avoid any effects of drying on the cells. Correct cytologic diagnosis can be made by examination of properly prepared aspiration cytology smears together with chest X-ray findings (figs. 3-13–3-15). Transbronchial curettage should be attempted for tumors invading the lung and bronchi (fig. 3-16) (32,102). The cytology of the pleural effusion may also disclose the phenotypic characteristics of thymoma cells. If possible, part of the material obtained should be kept frozen or fixed in cold acetone (4°C) and embedded in paraffin

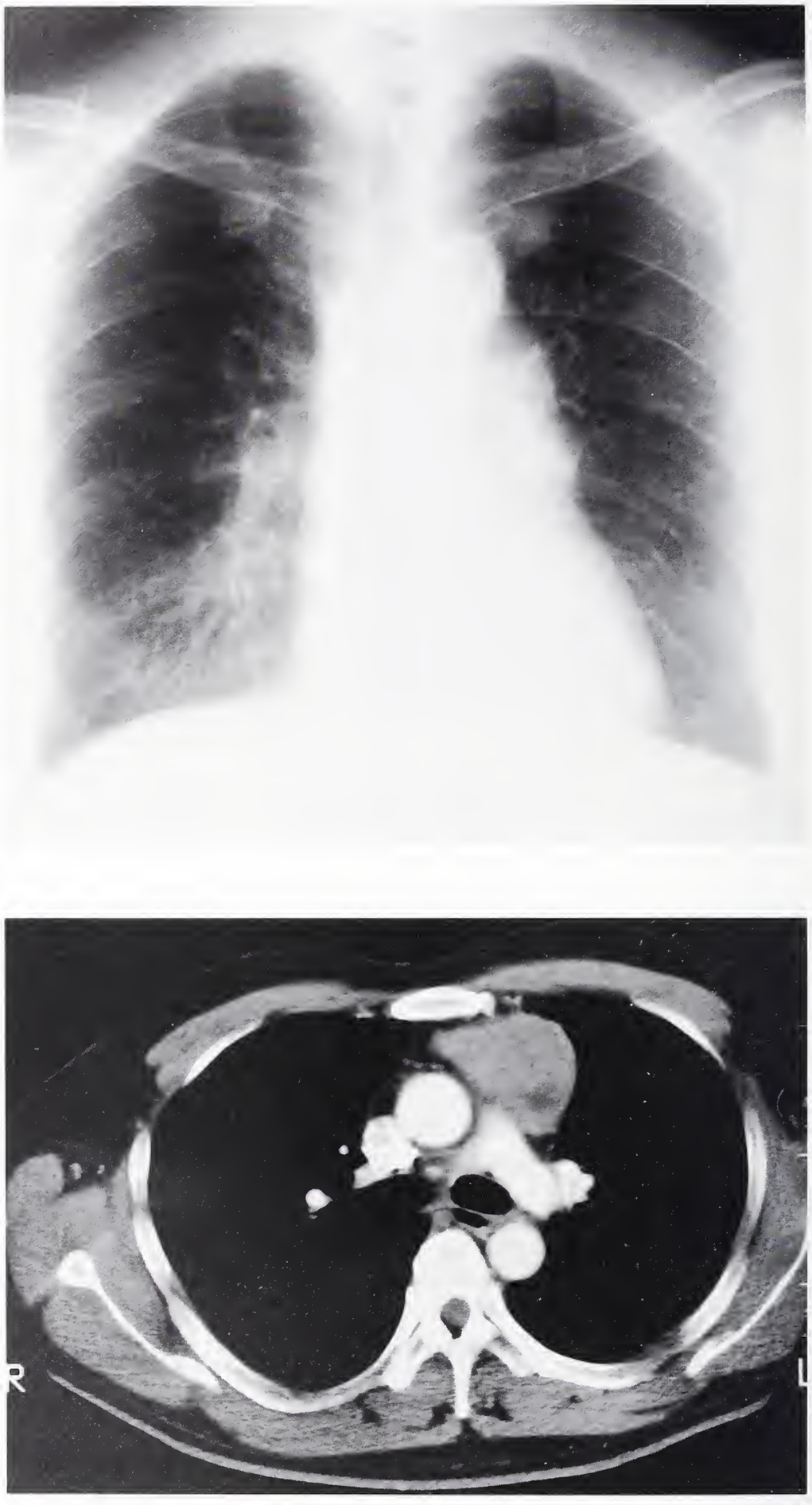


Figure 3-7
NONINVASIVE
THYMOMA

Top: Plain chest roentgenogram shows a well-defined tumorous density superimposed on the left pulmonary hilus and superior portion of the cardiac border.

Bottom: CT at the level of the tracheal carina reveals a clearly defined tumor with nonhomogeneous density between the sternum, ascending aorta, and truncus of the pulmonary artery, enhanced by radiopaque material. Note its smooth border facing the left lung.

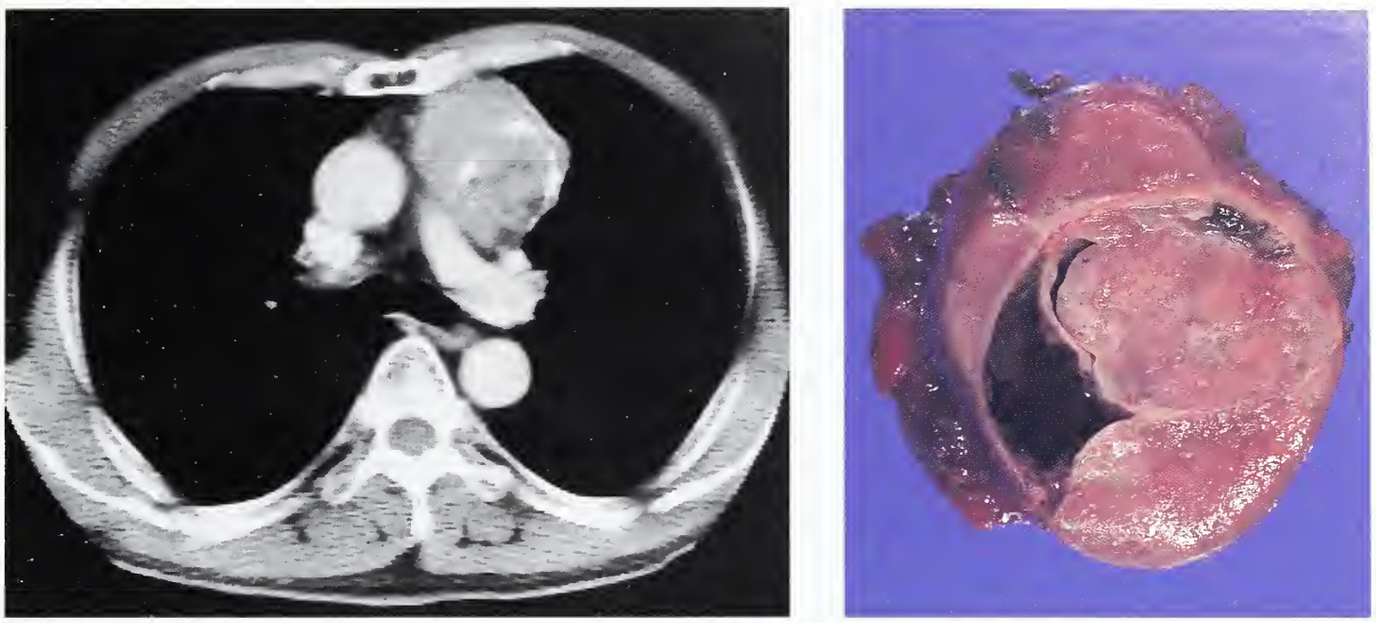


Figure 3-8
LOCALLY INVASIVE BUT CIRCUMSCRIBED THYMOMA WITH CALCIFICATION

Left: CT at the level of the tracheal carina reveals a well-defined tumorous density about 5 cm in diameter on the left side of the ascending aorta and adjacent to the left side of the pulmonary artery truncus, enhanced by radiopaque material. The nonhomogeneous tumor displaces the superior division of the left upper pulmonary lobe, and contains a ring-shaped calcification.

Right: Cut surface of the tumor reveals hemorrhage, cystic change, and invasive growth through a thick capsule with calcification.

for preservation of antigens, particularly the surface antigens of the constituent cells, both epithelial cells and lymphocytes (98).

The presence of epithelial cells, which are always positive for cytokeratin and frequently for CD57, and immature (cortical) T cells, which are positive for terminal deoxynucleotidyl transferase (TdT), CD1a, CD3, CD4, and CD8, is diagnostic of both encapsulated and invasive thymoma. Immature T cells are absent in thymic carcinoma, in which epithelial cells show variable immunohistochemical profiles depending on the histologic subtype (see Thymic Carcinoma). For germ cell tumors, tests should be made for the presence of placental alkaline phosphatase, alpha-1-fetoprotein, and beta-human chorionic gonadotropin; for lymphoma, common leukocyte antigen, and B-cell and T-cell markers should be checked.

Neither serum assay for tumor markers nor phenotype analysis of circulating lymphocytes is of value in establishing a diagnosis of thymoma. Of course, alpha-1-fetoprotein and beta-human chorionic gonadotropin should be checked when a malignant germ cell tumor is suspected.

Gross Findings. About one to two thirds of all thymomas are reported to be "encapsulated" or well circumscribed with "no gross invasion of adjacent structures or implants" (34,49,68,95). Of 73 evaluable surgically resected thymomas seen by the authors, 29 were completely encapsulated, 23 microscopically invaded through the capsule but were confined to the thymic tissue, 12 invaded the neighboring organs or tissue such as the lung, and 9 showed implantation to the pleura and diaphragm or metastasis to lymph nodes or distant organs. The size of the tumors varied from less than 2 to 20 cm in diameter. The smallest ones were less than 1 mm in diameter; these were invisible to the naked eye and were found incidentally in the thymus removed at the time of lung cancer surgery or autopsy. In one instance, three microscopic thymomas were found in the thymus of a single individual. Similar cases of multiple minute thymomas have also been reported (87). The average diameter of thymomas associated with myasthenia gravis was smaller than that of thymomas not associated. The average diameter of spindle cell type thymoma was larger than that of the polygonal cell type.

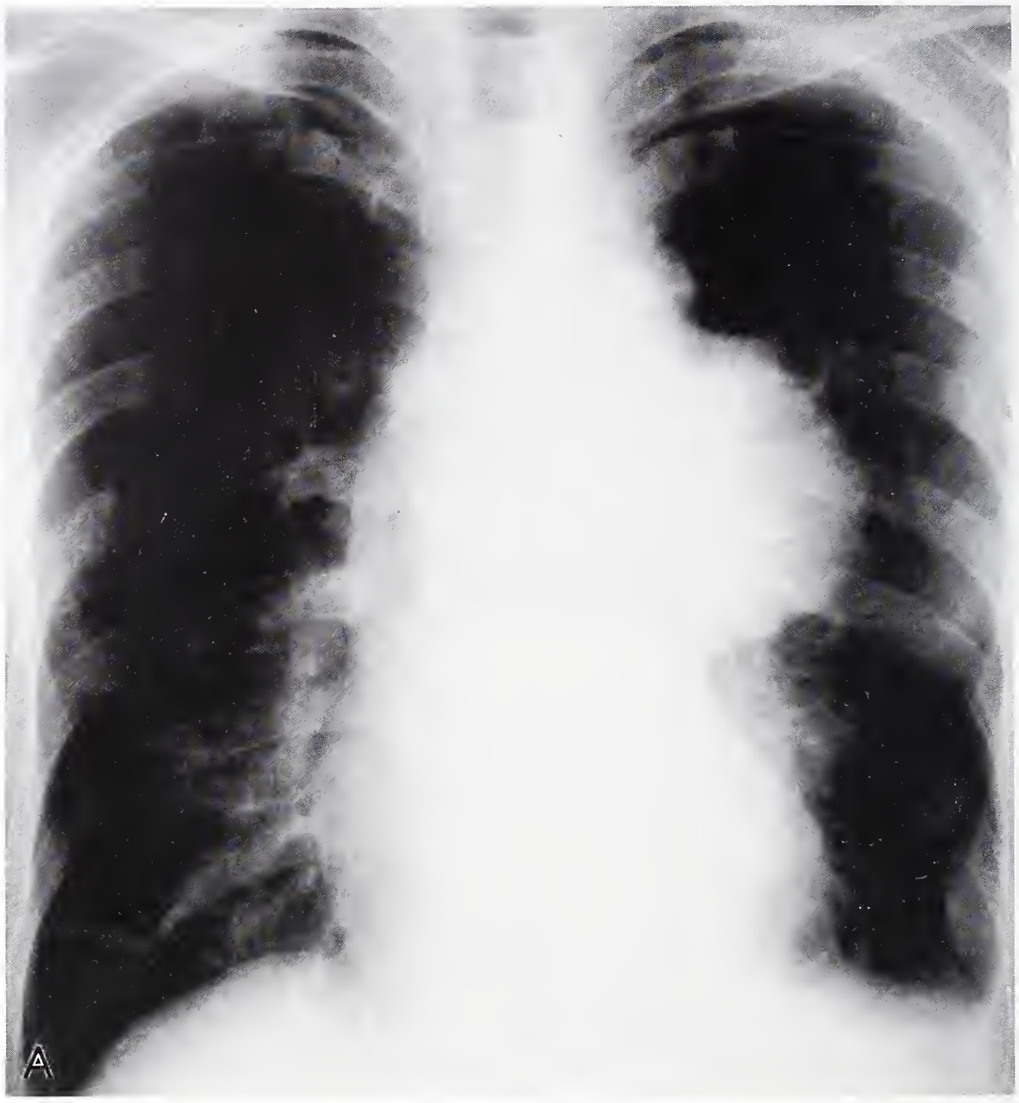
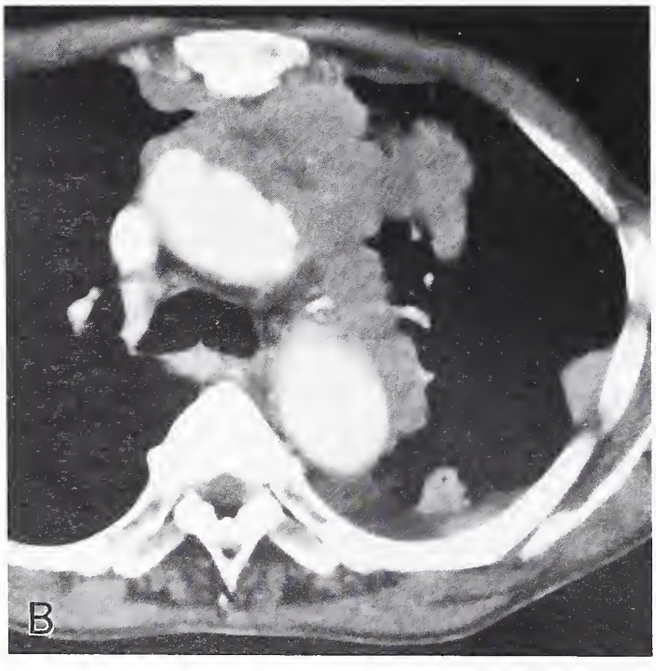


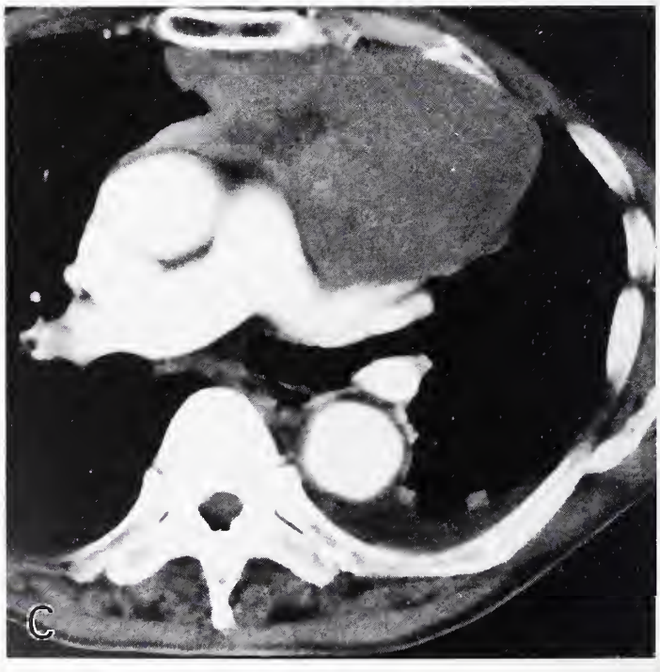
Figure 3-9
INVASIVE THYMOMA WITH PLEURAL IMPLANTATIONS

A: A tumor 7 cm in diameter projects into the left lung field and widens the mid-mediastinal density. Tumors convex toward the lung are seen scattered in the left lateral pleura, as is the left pleural effusion.

B: CT at the level of the tracheal carina discloses an irregular invasive growth of the anterior mediastinal tumor into the superior division of the left upper pulmonary lobe. Also seen are implanted tumors on the left parietal pleura with effusion.

C: CT 1 cm below the level of the tracheal carina reveals an irregular, nonhomogeneous, anterior mediastinal tumor enhanced by radiopaque material, which displaces posteriorly the ascending aorta, pulmonary artery truncus, and left pulmonary vein.





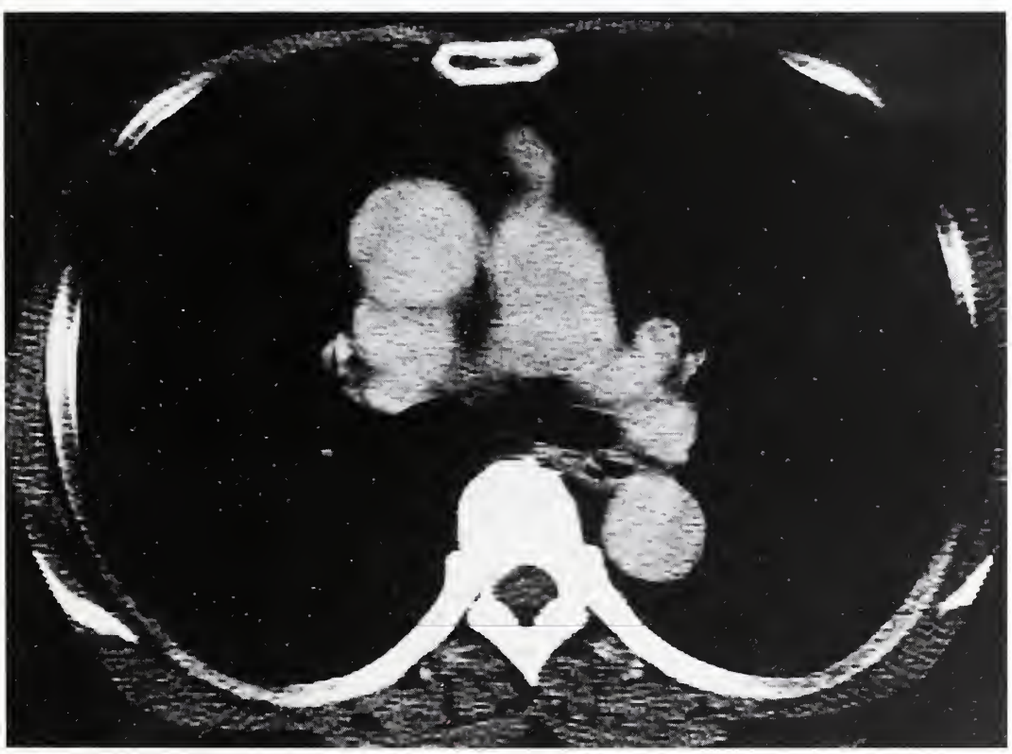


Figure 3-10
A SMALL THYMOMA DETECTED BY CT

Top: The ascending aorta protrudes towards the right lung, but there is no abnormal density in the mediastinum. (Lateral view revealed no abnormal density behind the sternum.)

Bottom: CT at the level of the tracheal carina discloses a tumorous density 1.5 cm in diameter in the fatty tissue of the anterior mediastinum anterior to the pulmonary artery truncus.

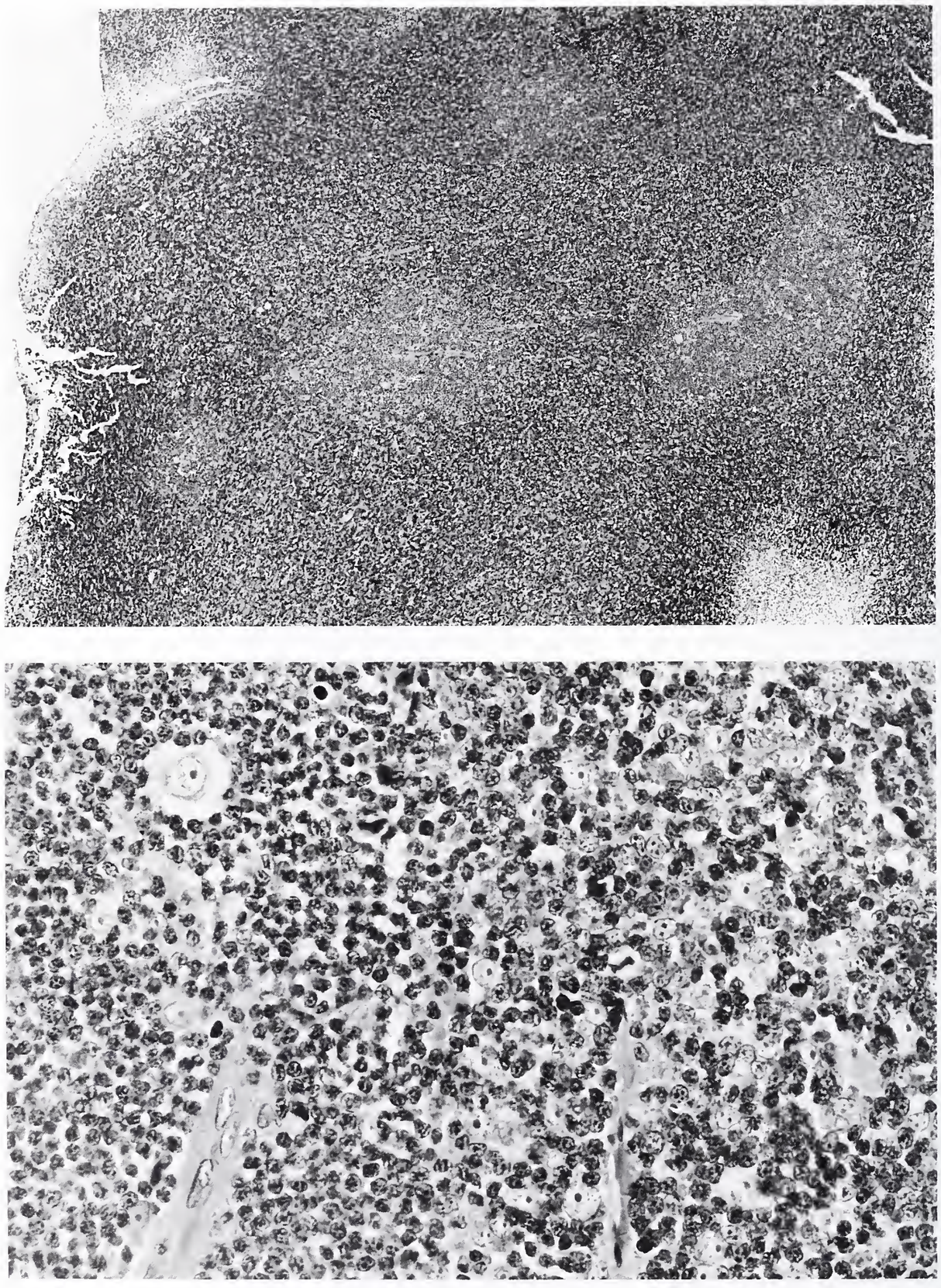


Figure 3-11
LYMPHOCYTE PREDOMINANT THYMOMA DIAGNOSED BY PERCUTANEOUS NEEDLE BIOPSY

Top: Almost the entire width of needle-biopsied tissue shows several lighter-stained areas of medullary differentiation.

Bottom: The border of the area with medullary differentiation reveals uniform, small mature lymphocytes and epithelial cells with or without prominent nucleoli in the "medullary" zone (left half of the figure) and an increased number of epithelial cells with distinct, round nucleoli and active lymphocytes in the "cortical" zone (right half of the figure). Immunostaining for cytokeratin (DAKO) in epithelial cells is shown in figure 3-76.

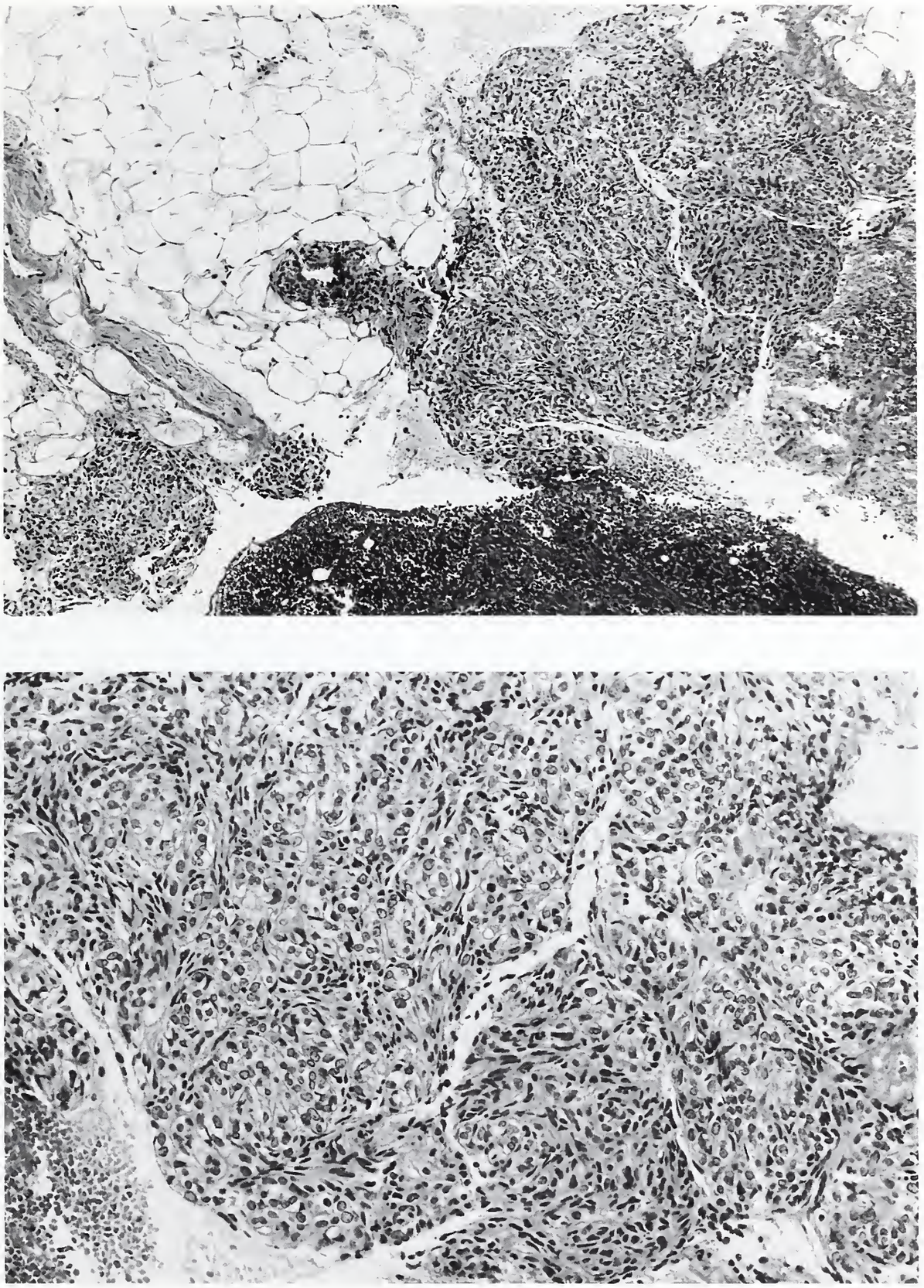


Figure 3-12
PREDOMINANTLY EPITHELIAL, SPINDLE CELL THYMOMA
DIAGNOSED BY PERCUTANEOUS NEEDLE BIOPSY

Top: Low-power magnification of a biopsy specimen shows fragments of tumor, fat, and blood.

Bottom: The tumor is composed of small lobules of oval to short spindle-shaped epithelial cells with bland nuclei and inconspicuous nucleoli. Lymphocytes are scanty.

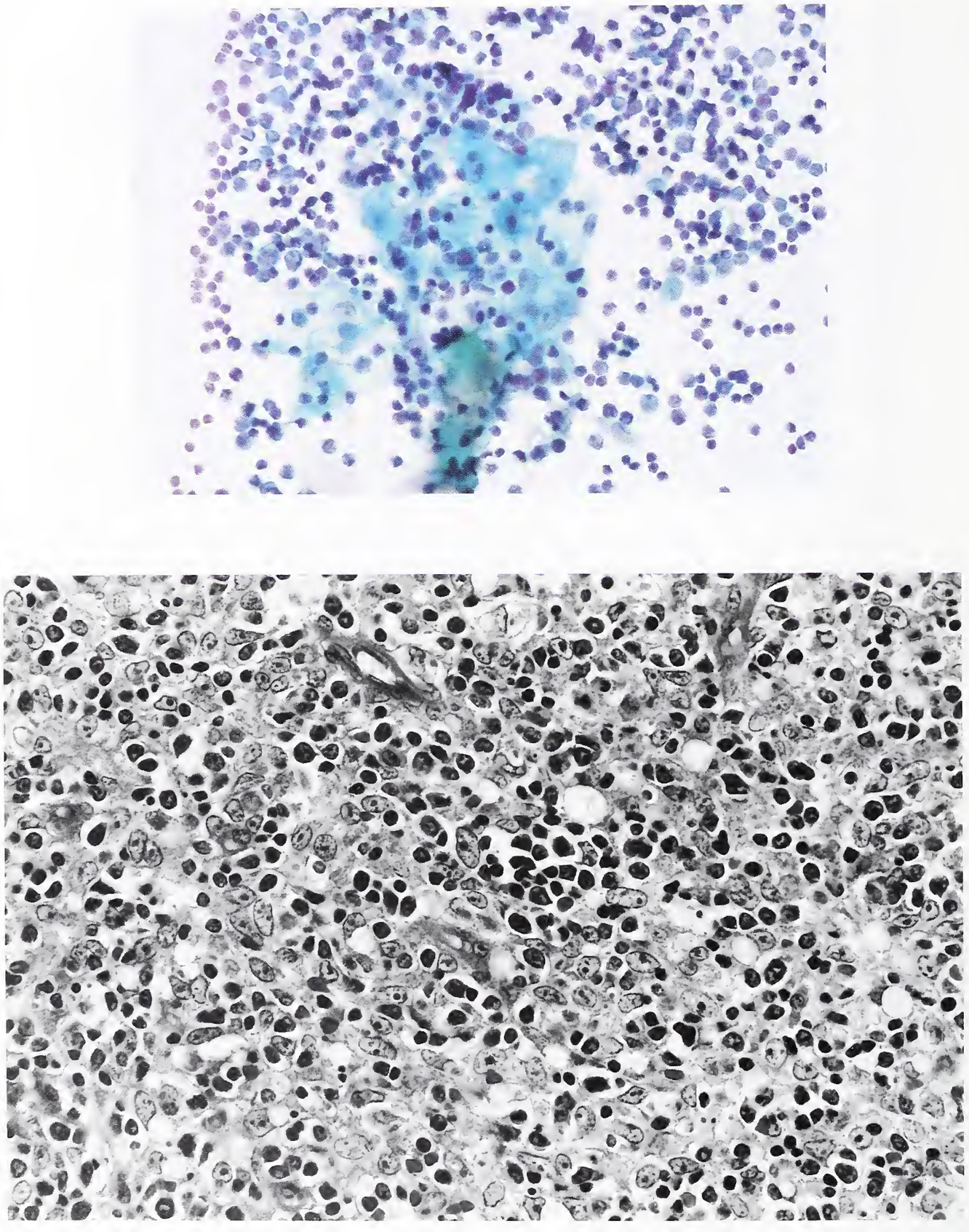


Figure 3-13
THYMOMA DIAGNOSED BY ASPIRATION CYTOLOGY

Top: Smear shows a clump of epithelial cells with oval nuclei possessing a fine chromatin pattern and prominent nucleoli surrounded by lymphoid cells. Together with X-ray findings, thymoma of the polygonal cell type was strongly suspected.

Bottom: Histology of the resected tumor discloses features characteristic of mixed lymphocytic and epithelial thymoma of the polygonal cell type.

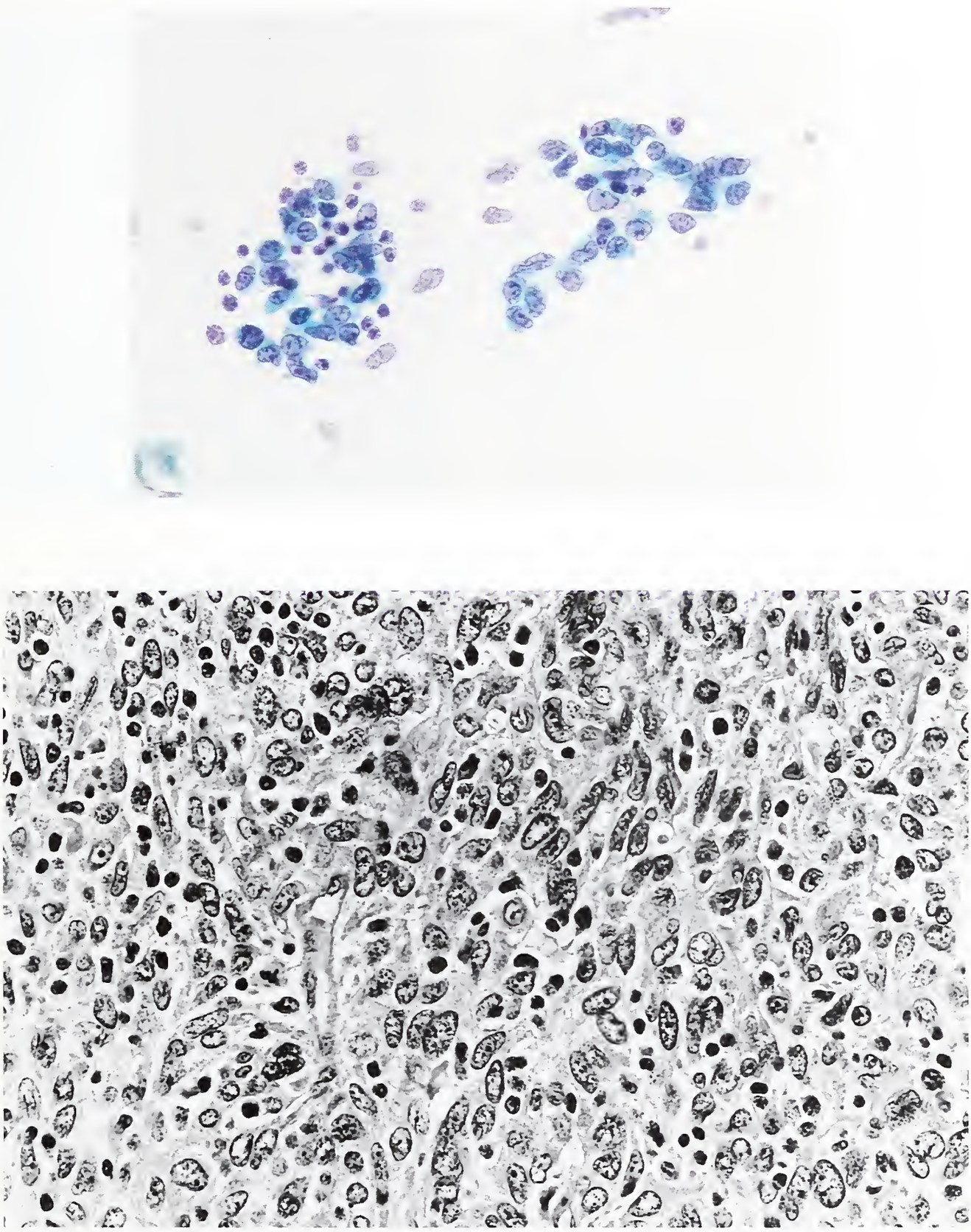


Figure 3-14
THYMOMA DIAGNOSED BY ASPIRATION CYTOLOGY

Top: Smear shows a mixture of lymphocytes and larger polygonal cells with somewhat vesicular, oval to irregular nuclei and some small nucleoli, consistent with thymoma of the mixed polygonal and spindle cell type.

Bottom: Histology of the resected tumor revealed a mixture of lymphocytes and epithelial cells of the polygonal and spindle cell types, which was consistent with a diagnosis of mixed thymoma.

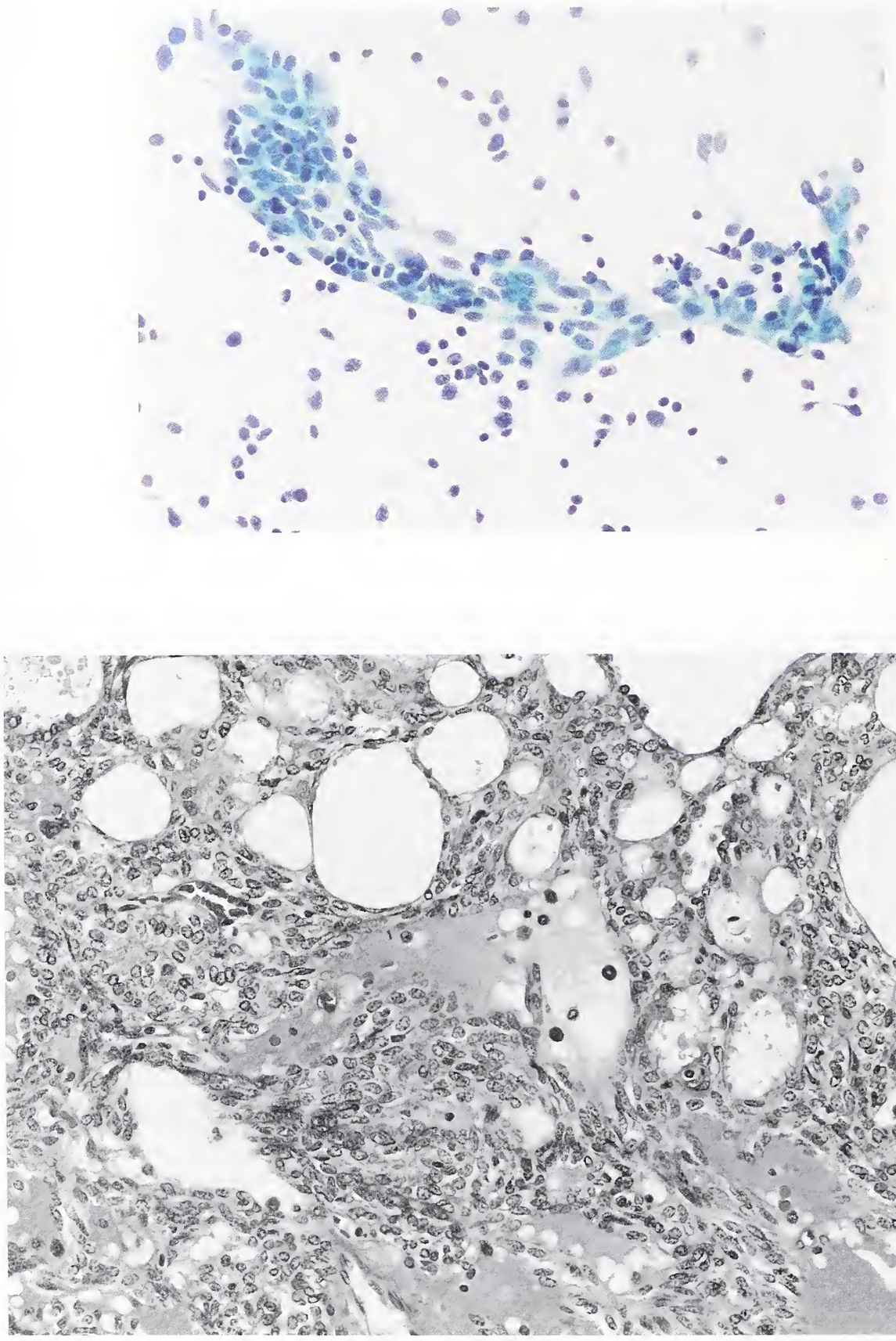


Figure 3-15
THYMOMA DIAGNOSED BY ASPIRATION CYTOLOGY

Top: Smear shows an aggregate of spindle-shaped cells and lymphocytes, strongly suggestive of thymoma of the spindle cell type.

Bottom: Histology of the resected tumor shows features characteristic of cystic thymoma composed predominantly of spindle-shaped epithelial cells.

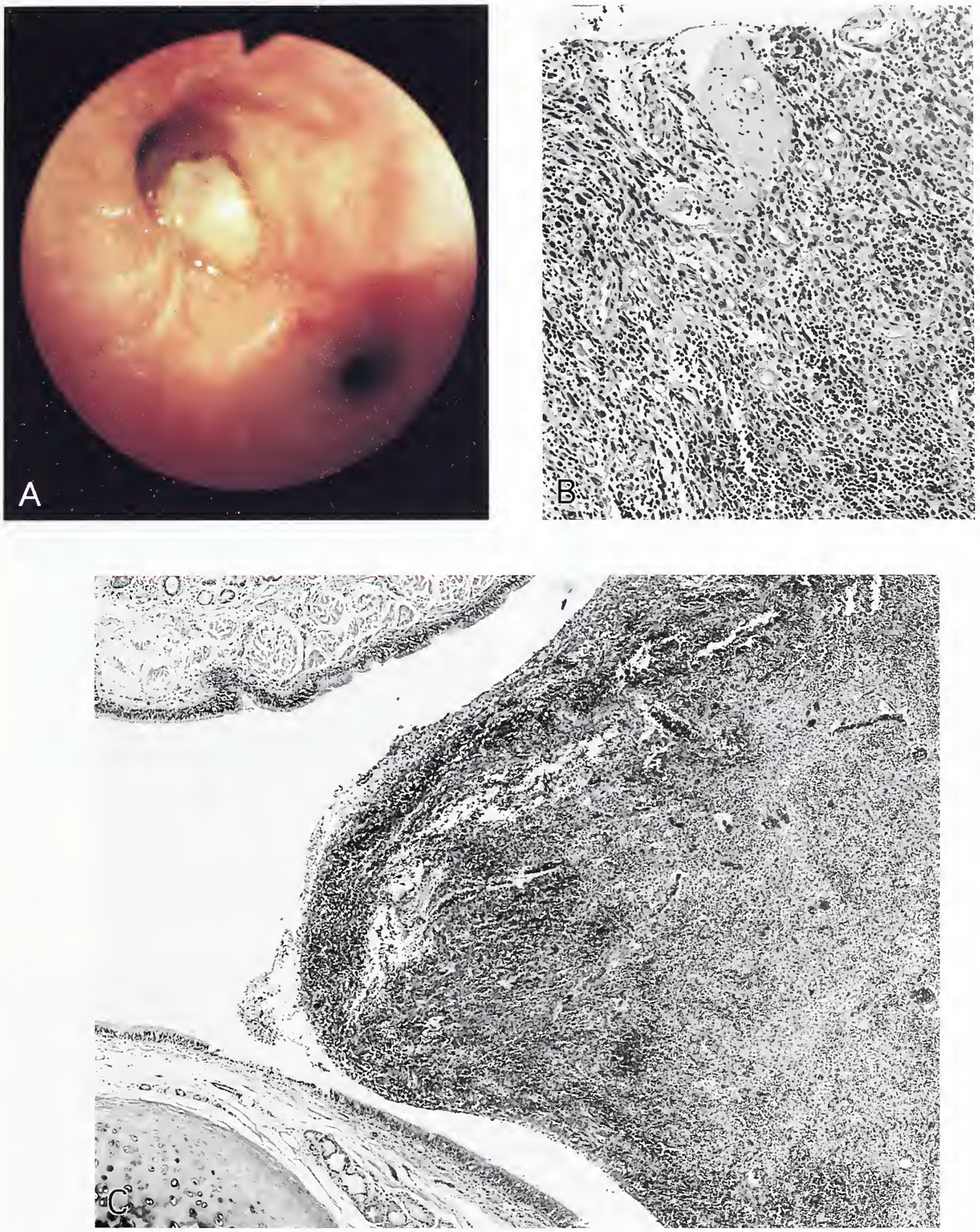


Figure 3-16
THYMOMA INVADING THE LUNG DIAGNOSED BY TRANSBRONCHIAL BIOPSY

A: Fiberoptic bronchoscopy reveals a polypoid tumor projecting into the left B3 bronchus.

B: The transbronchial biopsy specimen consists of lymphoid cells and larger, lighter-stained epithelial cells with a few perivascular spaces showing hyalinization. A diagnosis of thymoma of the mixed lymphocytic and epithelial type was made.

C: Surgically resected specimen (see figure 3-22) reveals a tumor projecting into the bronchial lumen. Immunostaining of a frozen section revealed frequent CD1a+, CD3+, and CD4 or CD8+ lymphocytes, confirming the diagnosis of thymoma.

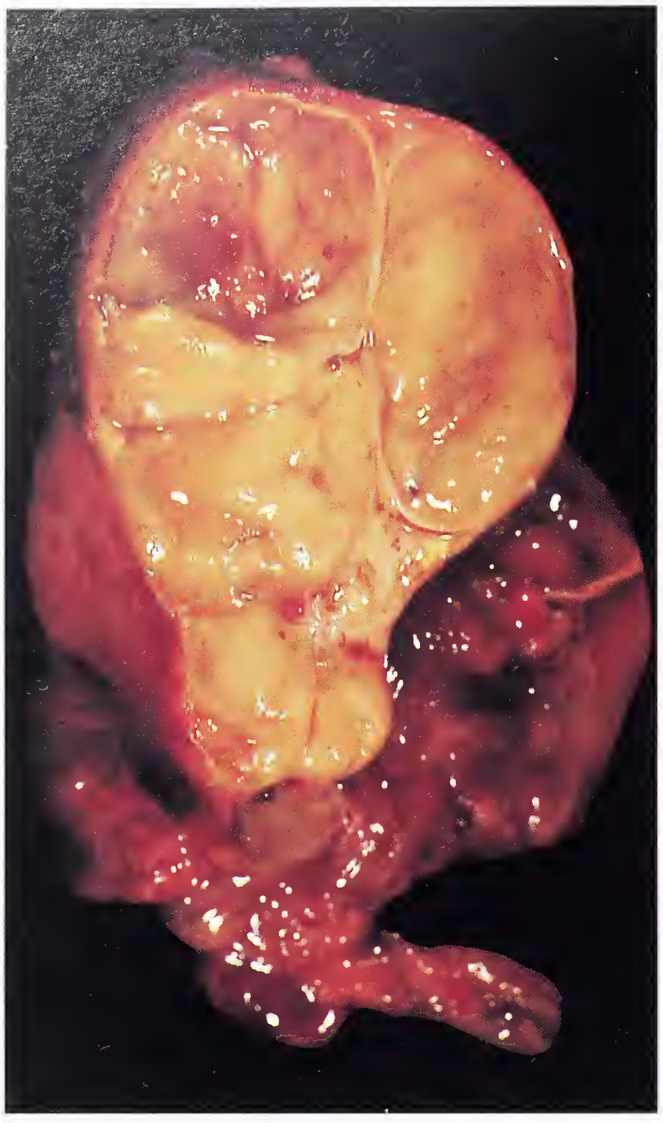


Figure 3-17
ENCAPSULATED THYMOMA
(MIXED LYMPHOCYTIC AND EPITHELIAL)
A bottle-shaped tumor is encapsulated and shows a bulging, rather homogeneous, faintly lobulated ivory-colored cut surface.

Thymoma may be round or oval with a smooth external surface, sometimes with attached fatty thymic tissue, or it may be irregularly nodular or bosselated resulting from division of the thymoma tissue into various-sized lobules by fibrous tissue (figs. 3-17–3-19). Calcification and, less frequently, ossification may be present in the fibrous capsule or septa dividing the lobules. Rarely, a plaque-like tumor may extend from the thymus inferiorly along the anterior thoracic rib cage. The area should be carefully examined grossly for evidence of transcapsular invasion, direct invasion of neighboring organs or tissue, and areas of tumor exposure due to incomplete removal.

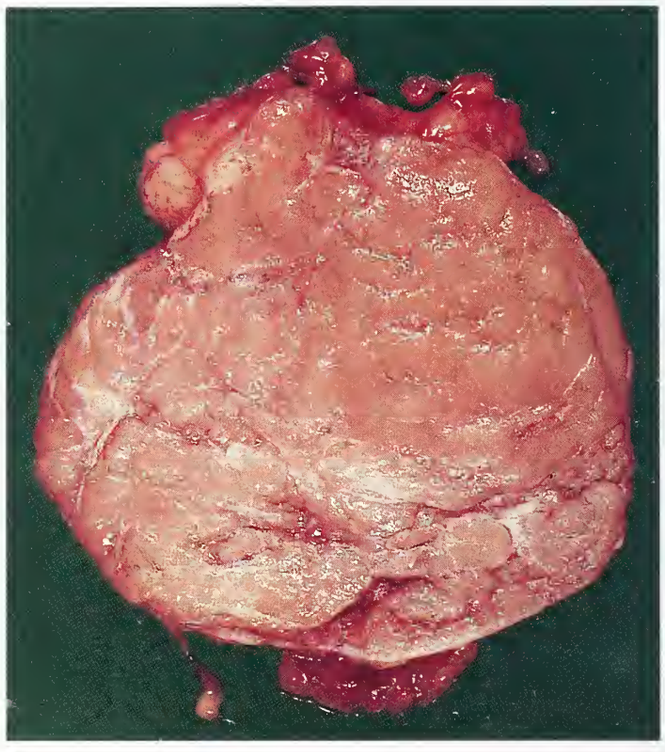


Figure 3-18
ENCAPSULATED THYMOMA (PREDOMINANTLY EPITHELIAL, SPINDLE CELL TYPE)
An oval tumor is completely encapsulated, with a pale tan, bulging, irregularly lobulated cut surface.

The cut surface of thymoma is pale tan or pinkish gray and often lobulated; lobulation is the most characteristic feature and present in most cases. However, lobulation is absent in a few thymomas regardless of the degree of lymphocytic infiltration. Cystic changes are frequently seen, and cysts vary from very small and barely recognizable, containing clear fluid to large ones filled with blood or yellowish brown grumous material (figs. 3-20, 3-21). In rare cases, almost the entire tumor may become cystic with irregular trabeculae on the inner surface (104). Such a tumor should be examined carefully for any remnant of thymoma tissue, and examination of multiple blocks may be necessary to prove the cystic nature of the lesion. Foci of coagulation necrosis may be seen, but are infrequent. The presence of coagulation necrosis does not necessarily indicate a malignant nature, although it is more frequent and more extensive in thymic carcinoma (type II malignant thymoma) than in invasive thymoma (type I malignant thymoma). Hemorrhage is also seen in some thymomas, in most instances due to surgical manipulation of the tumor.

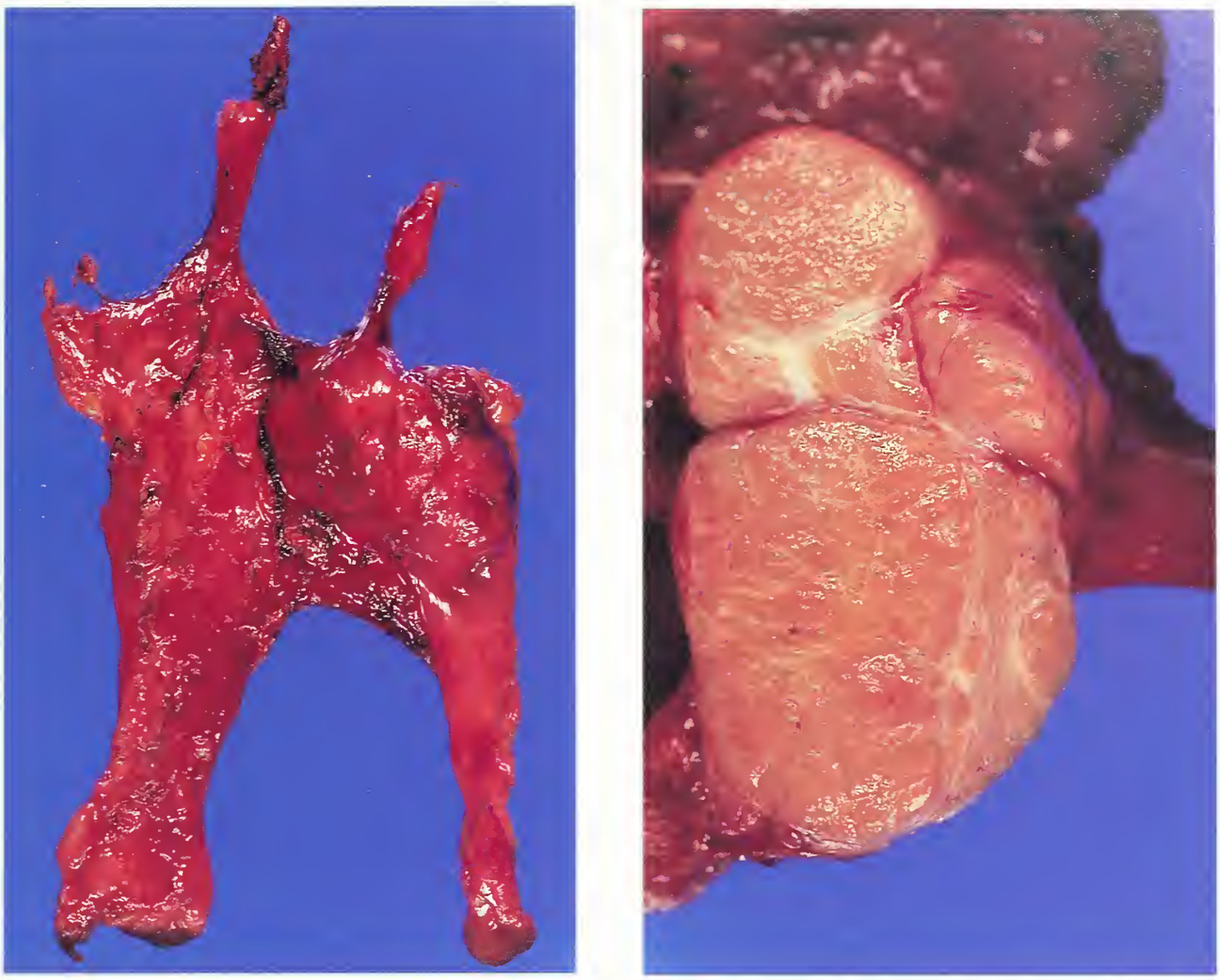


Figure 3-19
LOCALLY INVASIVE, CIRCUMSCRIBED THYMOMA
(MIXED LYMPHOCYTIC AND EPITHELIAL AND MIXED POLYGONAL AND SPINDLE)

Left: The tumor is present in the left lobe of the thymus.

Right: Its cut surface bulges, and is pale tan and faintly lobulated. It invaded the capsule at a few points but still remained within the thymus.

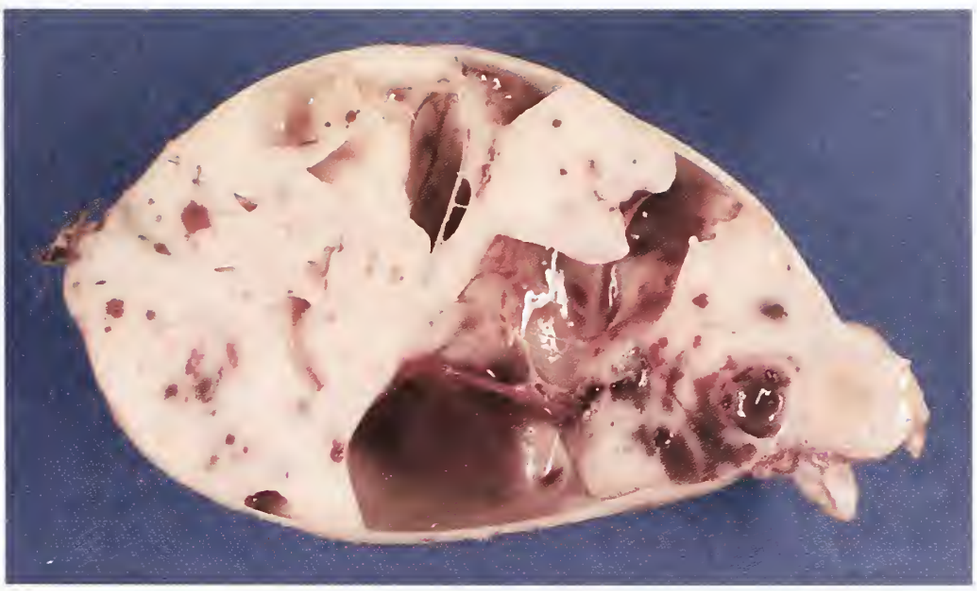


Figure 3-20
ENCAPSULATED
CYSTIC THYMOMA

Post-formalin-fixed cut surface reveals an ivory-colored tumor with multiple cystic spaces varying from pin-head sized to a few centimeters in diameter. Small hemorrhages are also noted.

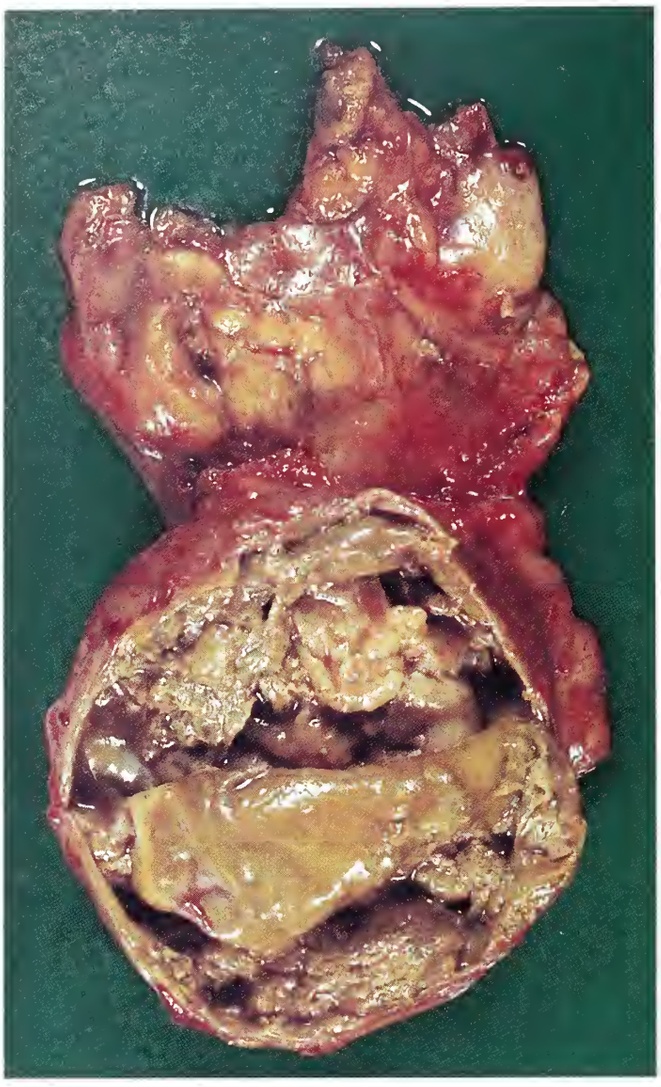


Figure 3-21
ENCAPSULATED CYSTIC THYMOMA
(PREDOMINANTLY LYMPHOCYTIC)

A tumor encapsulated by a thick capsule contains brown liquid and necrotic material. The lining is smooth in part and irregular in part with excrescences of necrotic and viable tumor tissue.

Figure 3-22
THYMOMA, MIXED LYMPHOCYTIC AND EPITHELIAL, INVADING THE LUNG PARENCHYMA AND A BRONCHUS

An irregularly shaped tumor is lobulated in part and nodular in part with a distinct border at the front invading the lung tissue. A small polypoid projection into the left B1+2 bronchus is noted in the left lower corner of the tumor cut surface (same case as that in figure 3-16).

Two or more separate nodules of thymoma may be found in a thymus. We have seen a case with multiple nodules of both thymoma and thymic carcinoma, with some nodules showing transitional features between the two (see figs. 3-107, 3-116) (79). Bernatz et al. (35) reported three cases in which multiple thymomas were present.

Grossly, thymoma invading the lung or other adjacent structures may also be lobulated and even partly encapsulated at the site of invasion, although the advancing borders are not always distinct and even at times blurred (figs. 3-22, 3-23). Tumors implanted on the pleura, pericardium, and diaphragm are similar to the primary tumor, as are metastatic foci in lymph nodes and distant organs. However, lobulation may be less distinct than in the primary, due probably to reduction in the amount of fibrous tissue (fig. 3-24).

Microscopic Findings and Subtypes. The majority of thymomas are either completely or partially encapsulated by a fibrous capsule of varying thickness, which connects with dense fibrous bands within the tumor that divide it incompletely into lobules (fig. 3-25). The capsule may contain calcium deposits, but ossification is rare (fig. 3-26). Since a capsule is absent in microscopic thymomas found incidentally in routine sections of the thymus taken at the time of lung and

Figure 3-23
INVASIVE THYMOMA
(LYMPHOCYTE PREDOMINANT)

About half of the tumor is in the mediastinum and the rest in the upper lobe (S1+2, S5) of the left lung. The cut surface shows faint lobulation, areas of hemorrhage, and nodular infiltrative borders. The borders are sharply defined in areas and blurred in areas.

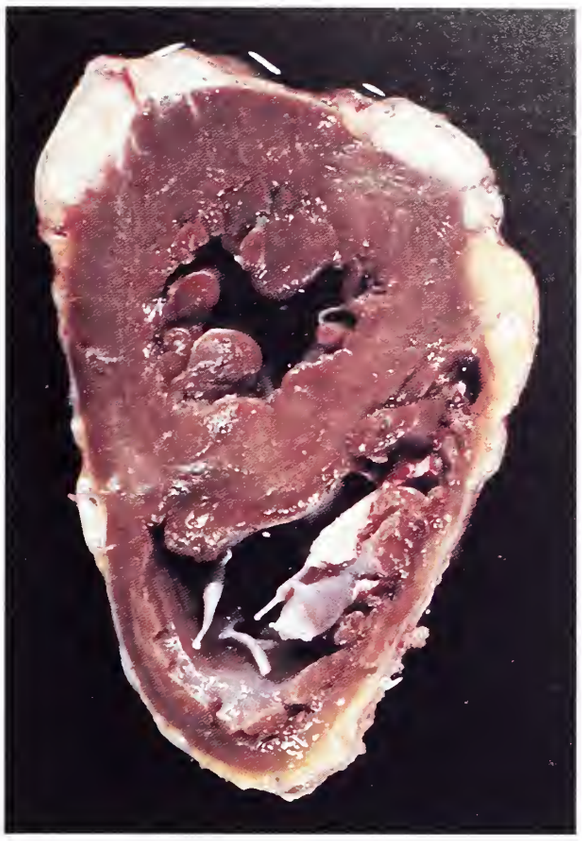


Figure 3-24
THYMOMA IMPLANTED ON THE PERICARDIUM

This ivory-colored, faintly lobulated tumor obliterated the pericardial sac and invaded into the myocardium at the anterior and posterolateral border of the left ventricle. Histologically, it was of the mixed lymphocytic and epithelial, and polygonal cell type.

cardiac surgery or at autopsy (figs. 3-27–3-29) (87,92), one should assume that capsule formation is the result of the host's defense mechanism, and that it reflects the growth properties of the tumor. That is, the slower the tumor growth, the thicker and more complete the capsule. A capsule is also found at the advancing border of a tumor invading the lung and in implantation metastasis (fig. 3-30). Lack of a capsule at the advancing border may indicate a tumor with accelerated growth, since it appears more frequently in thymoma of the predominantly polygonal (round or oval) epithelial cell type (fig. 3-31). At times, the thick fibrous capsule is invaded by the tumor, which may bud outside the capsule into non-neoplastic thymic tissue and extend into the lobules of the non-neoplastic thymus (figs. 3-32, 3-33). Encapsulation of such budding may be seen occasionally (fig. 3-34). For staging purposes, tumors with encapsulated buds must be considered either encapsulated or invasive.

The lobules of a thymoma subdivided by fibrous trabeculae vary in size and shape, are often irregular in outline, and have distinctive borders in many instances (fig. 3-35). However, the boundaries may be blurred, particularly in cases of mixed polygonal and spindle cell thymoma, where the fibrous trabeculae themselves are composed of spindle-shaped neoplastic epithelial cells with a fibroblast-like appearance (fig. 3-36).

Figure 3-25
ENCAPSULATED THYMOMA

The tumor is encapsulated by thick collagenous tissue and subdivided into irregular lobules by fibrous tissue. Atrophic thymic tissue is attached to the capsule.

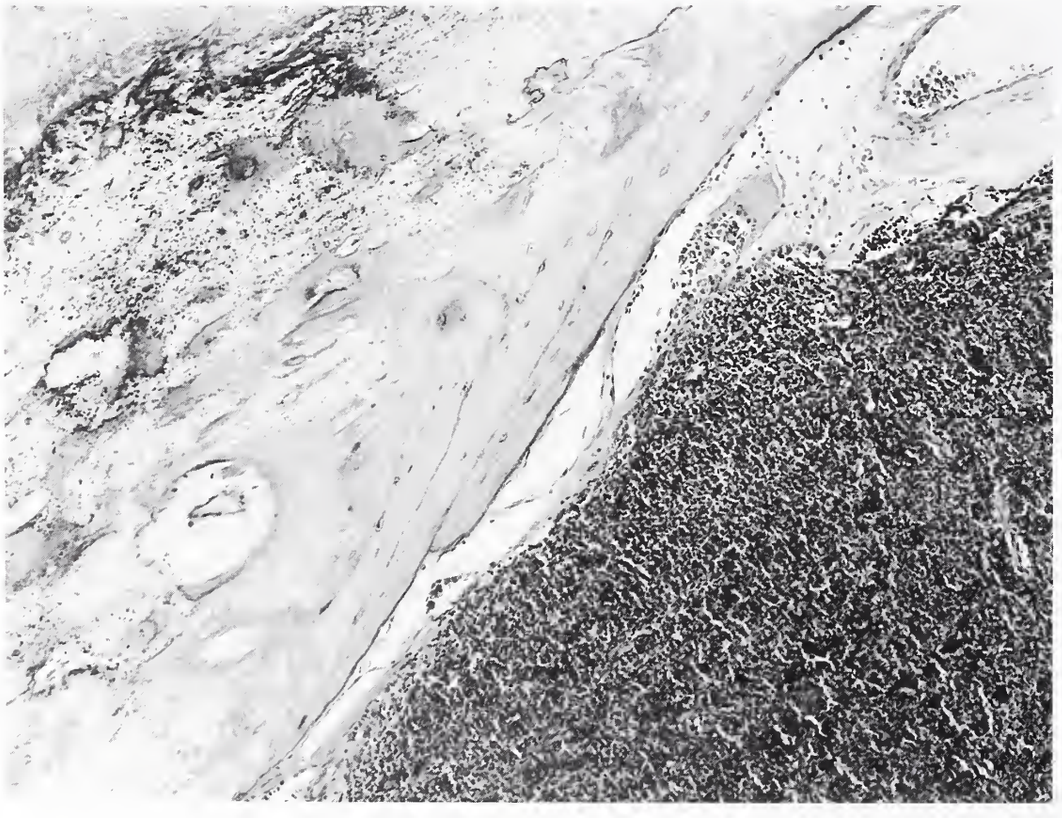


Figure 3-26
OSSIFICATION IN THE CAPSULE OF THYMOMA

Ossification with calcification is evident in capsule of lymphocyte predominant thymoma of polygonal cell type.

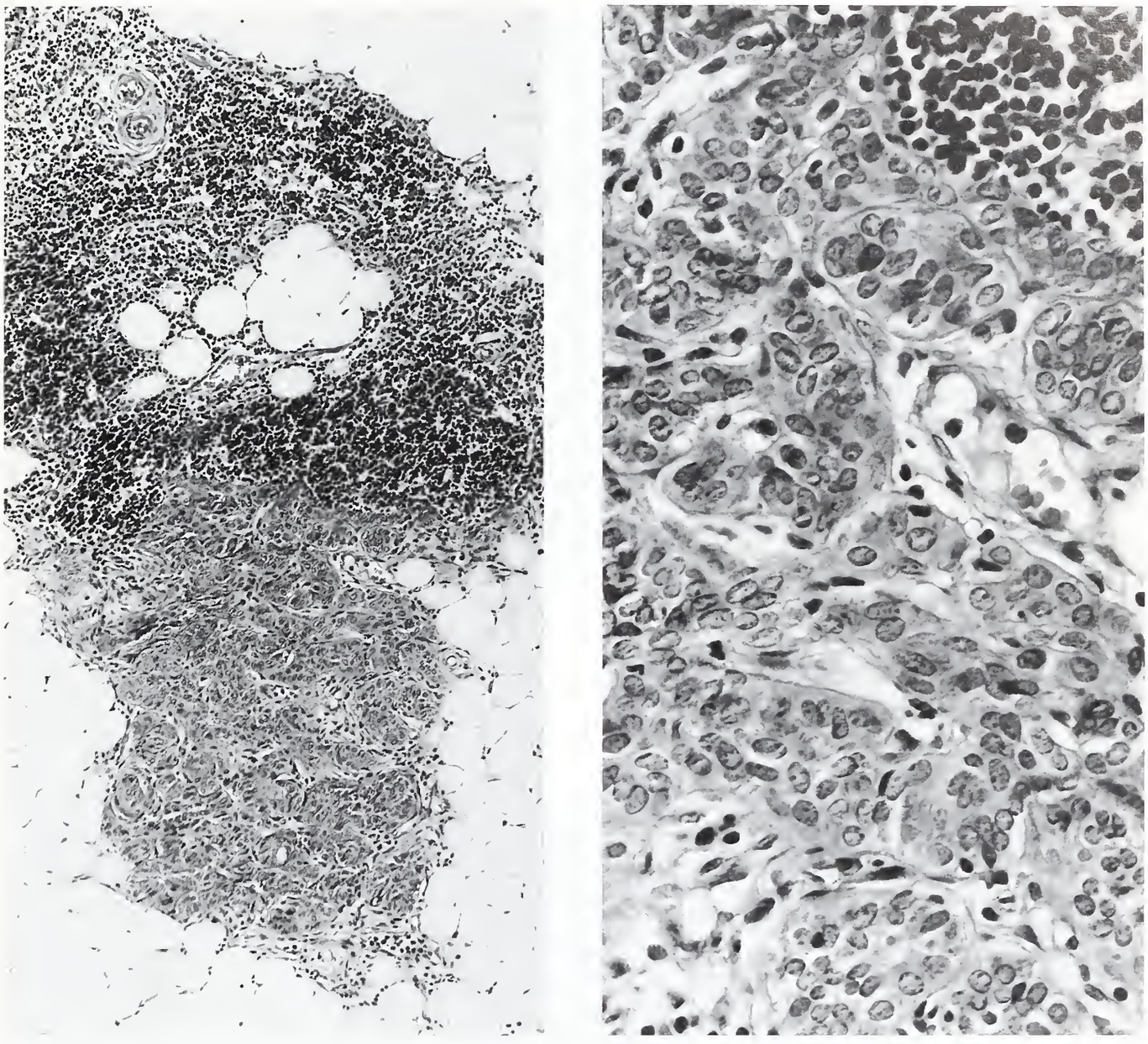


Figure 3-27
MICROSCOPIC THYMOMA

Left: In continuity with the cortex of the thymus, there is a microscopic lesion consisting of small, solid epithelial cell nests with a scanty fibrous stroma.

Right: Higher magnification reveals the epithelial cells to be polygonal with oval uniform nuclei, indistinct nucleoli, and scanty cytoplasm. (Courtesy of Dr. Tetsuro Kodama, Matsudo City, Japan.) (Figures 3-27 and 3-28 are from the same case.)

Another characteristic histologic feature seen in about two thirds of all thymomas is the formation of perivascular spaces. These are formed and bordered by often palisading epithelial cells with a basement membrane. They contain mature lymphocytes of both B-cell and T-cell types, plasma cells, mast cells, and plasma fluid. They vary in size from minute, recognizable only by careful observation, to as large as 1 mm in diameter. Near the center, a small vessel, probably a capillary or postcapillary venule, can be identified (figs. 3-37–3-39). The spaces may contain foamy macrophages and show a tendency to hyalinize. Hyalinization of the spaces usually begins with exudation of fibrinous materials into them, followed by gradual hyalinization and obliteration of the spaces (figs. 3-40–3-42).

Perivascular spaces can be seen in both polygonal (round or oval) cell type and spindle cell type thymomas, but are much more frequent in the

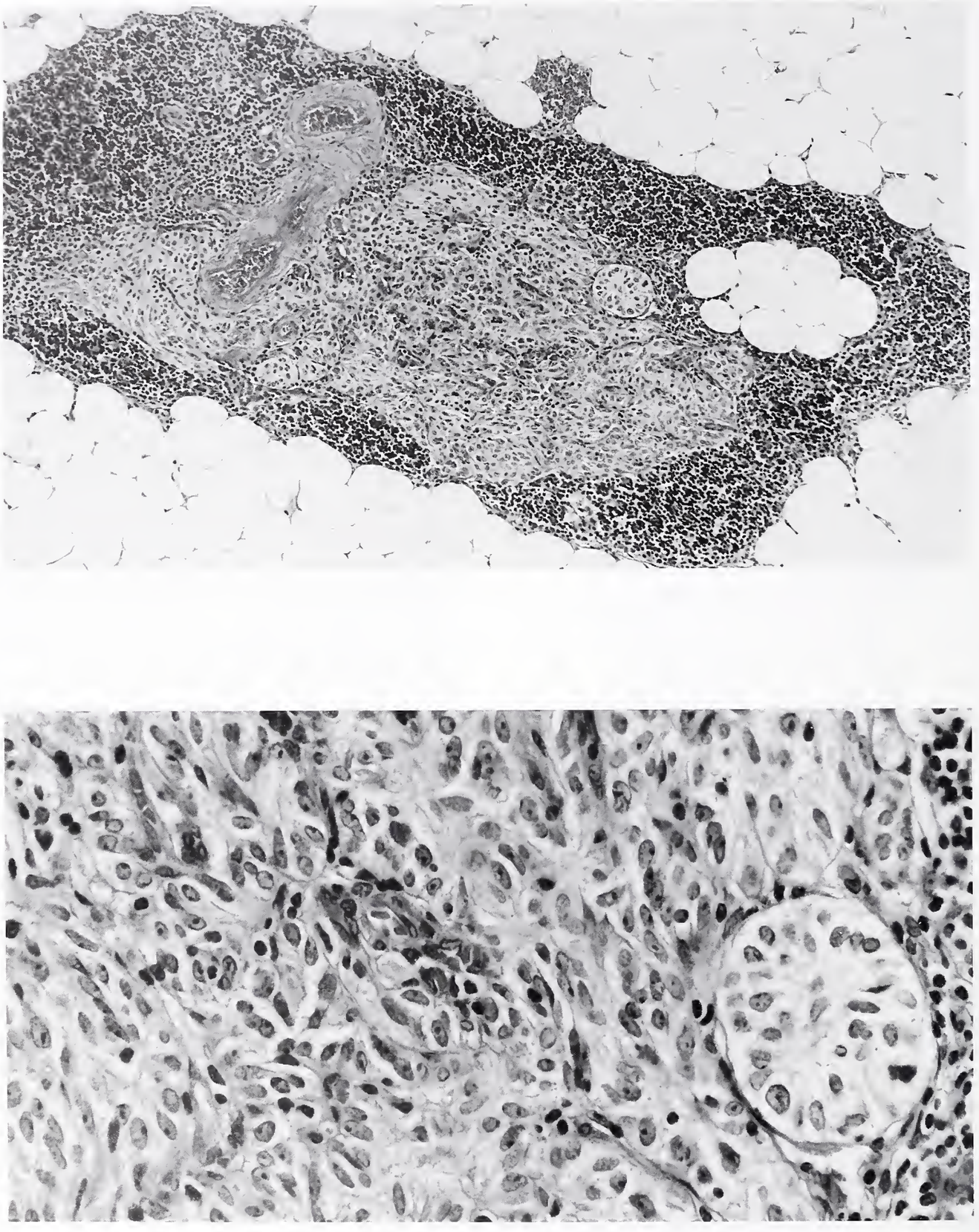
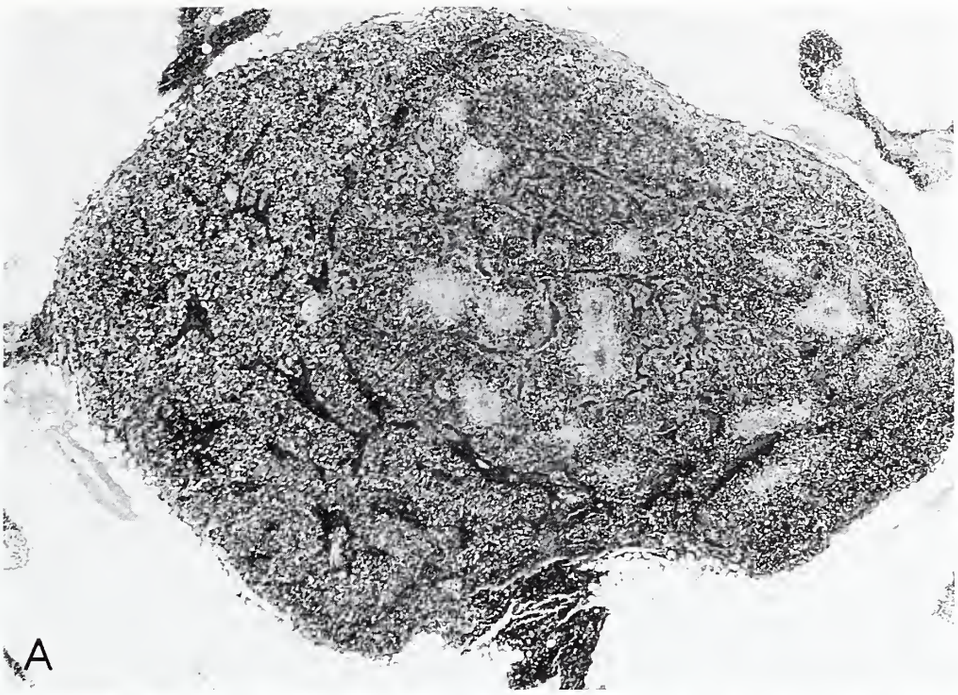


Figure 3-28
MICROSCOPIC THYMOMA

Top: Another microscopic lesion occupies the central portion of the thymic lobule and is surrounded by the cortex. A small amount of the medulla is noted in the left upper portion of the figure adjacent to the lesion.

Bottom: Higher magnification of the microscopic lesion reveals that the constituent cells are short and spindled with oval to elongated uniform nuclei, and some small but distinct nucleoli. A single rosette-like structure is noted. (Courtesy of Dr. Tetsuro Kodama, Matsudo City, Japan.)



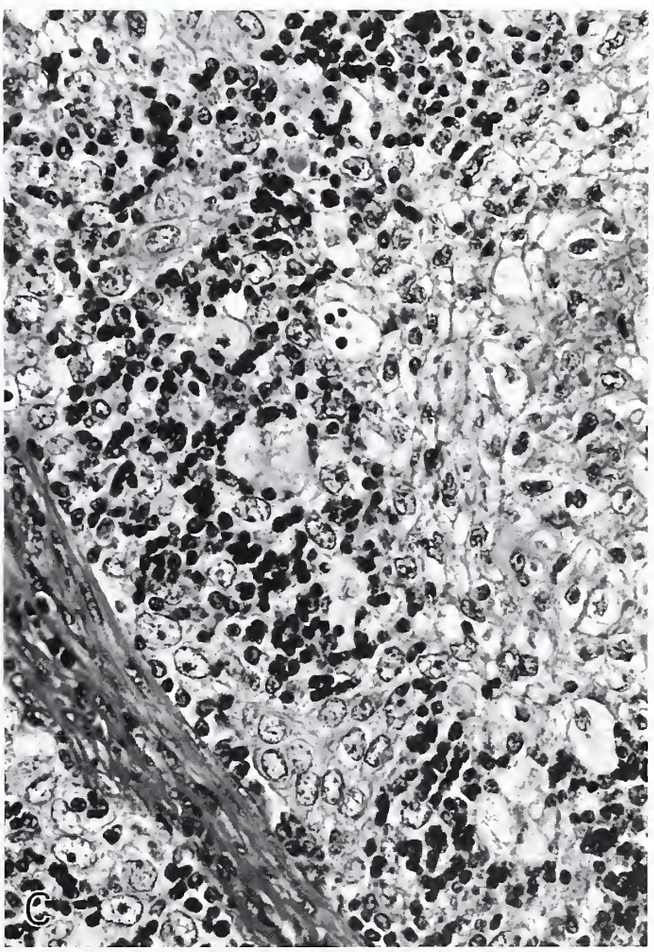


Figure 3-29
INCIDENTALLY FOUND SMALL THYMOMA WITH EPIDERMOID FEATURES

A: The tumor is 5 mm in diameter and nonencapsulated, in which several clear areas with epidermoid features are scattered.

B: An area with epidermoid features is surrounded by a lymphocyte-rich zone with polygonal epithelial cells.

C: Higher magnification reveals transitional cells between the cells with epidermoid features and the polygonal epithelial cells with vesicular nuclei and prominent nucleoli.

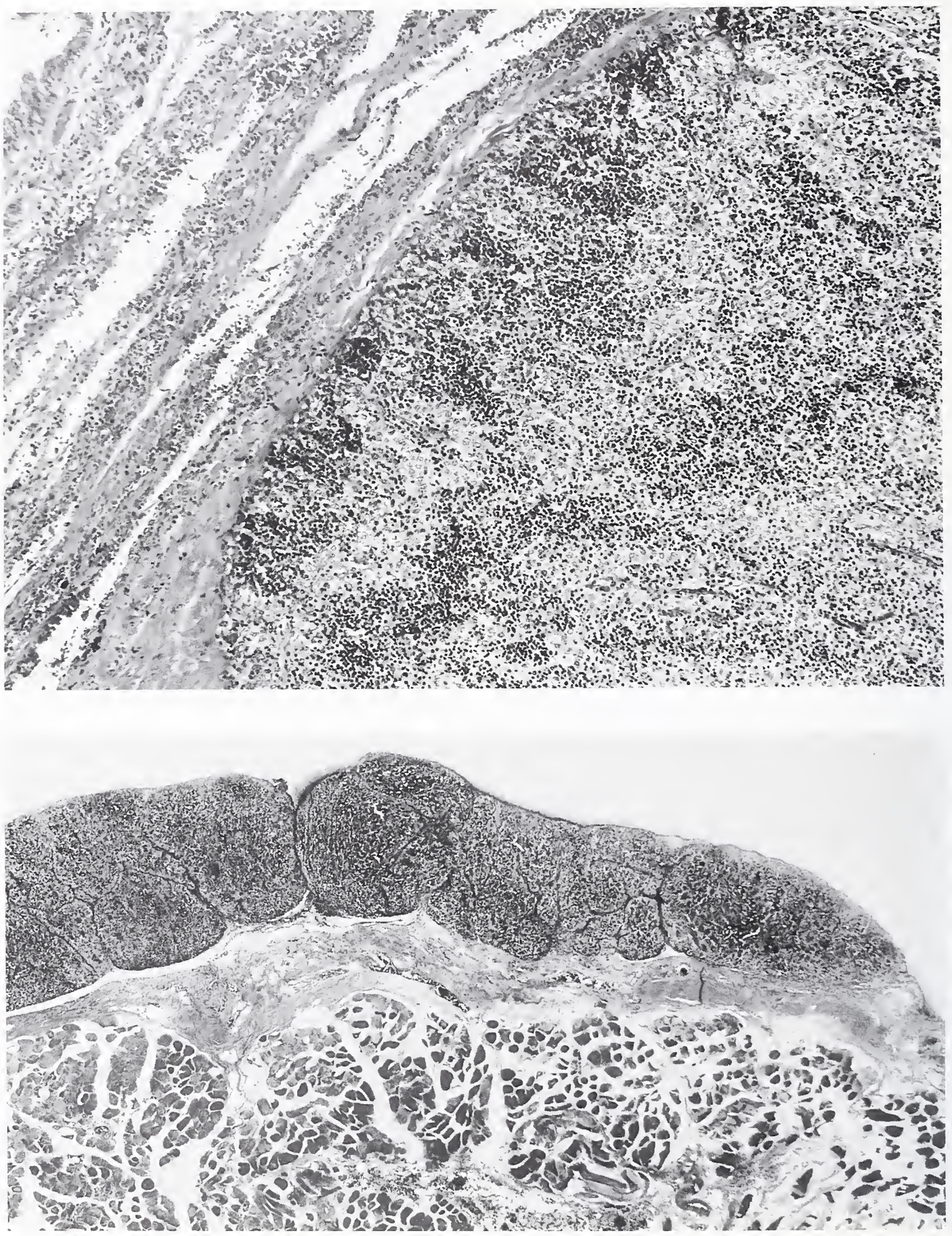


Figure 3-30

THYMOMA WITH INVASION INTO THE LUNG AND IMPLANTATION METASTASIS TO THE DIAPHRAGM

Top: Thymoma of the mixed lymphocytic and epithelial cell type has invaded the lung, where a thin collagenous capsule has formed.

Bottom: The tumor implanted on the diaphragm is lobulated and thinly encapsulated.

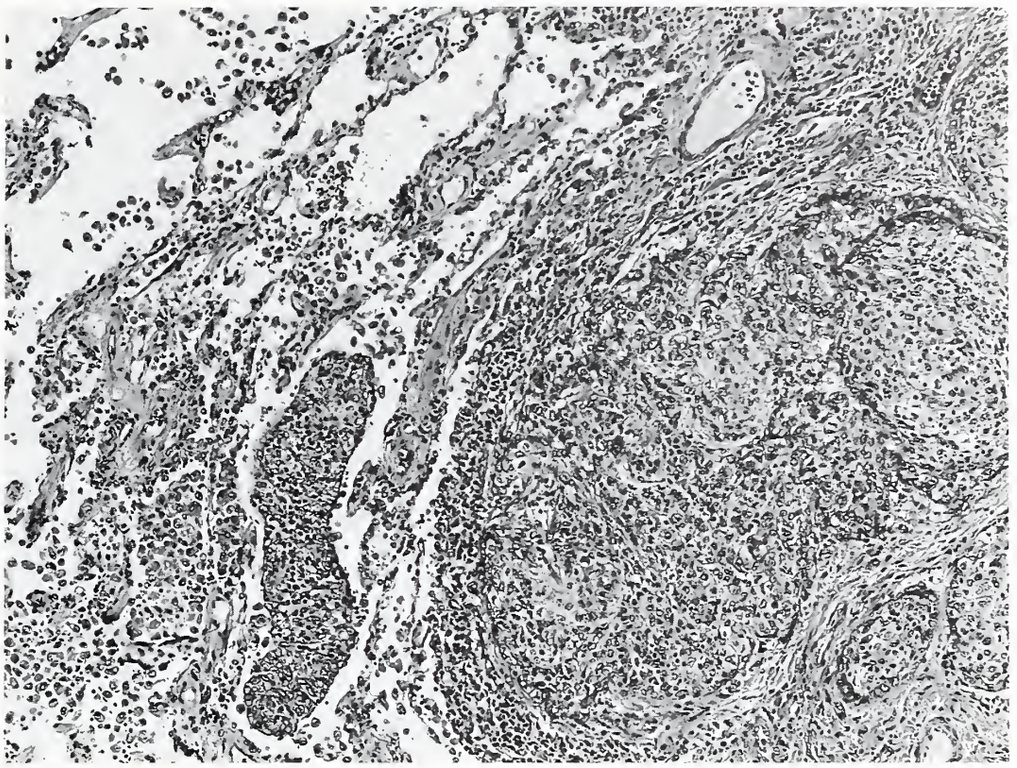


Figure 3-31
THYMOMA INVADING THE LUNG

At the advancing front of a thymoma of the predominantly epithelial and polygonal cell type with atypia, tumor nests are floating in alveoli without forming a fibrous capsule.

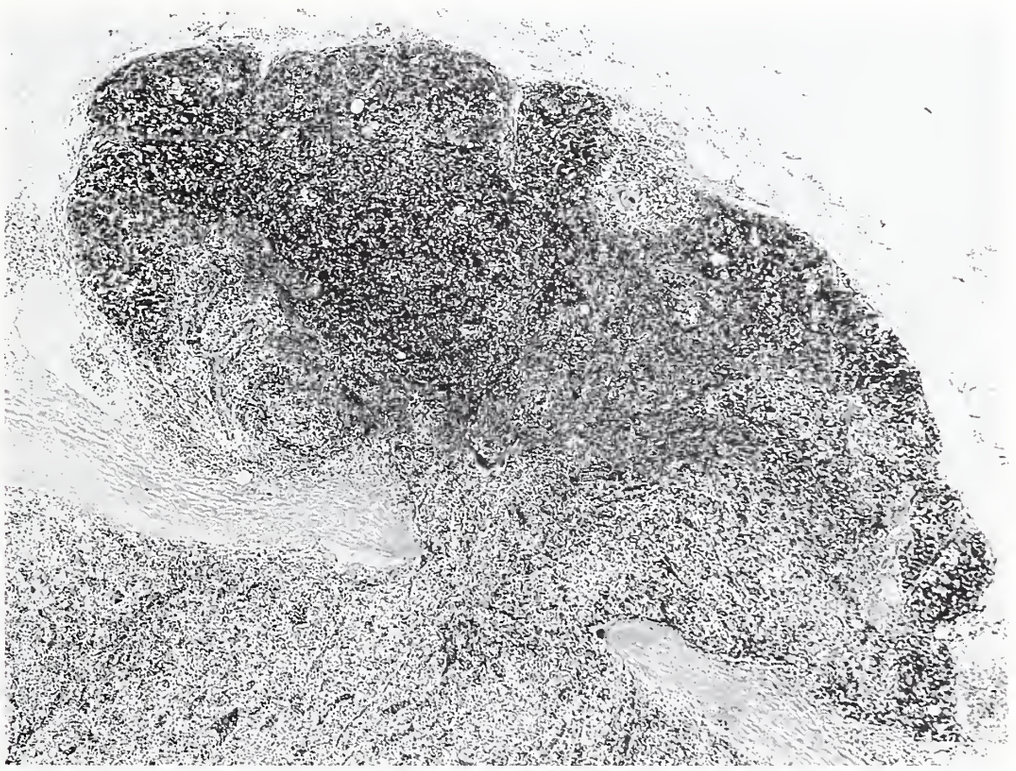


Figure 3-32
THYMOMA INVADING THE CAPSULE

A mushroom-shaped tumor results from invasion by the tumor of its own thick capsule. It involves non-neoplastic thymic tissue with a Hassall corpuscle at its apex.

Figure 3-33
THYMOMA INVADING THYMIC TISSUE OUTSIDE THE THICK CAPSULE

Thymic tissue attached to the fibrous capsule of a thymoma has been invaded by a thymoma of the polygonal cell type with distinct nucleoli, identical in histology to the main tumor. A minute thymoma is occasionally seen in extracapsular thymic tissue, which does not appear to be the focus of an independent tumor.

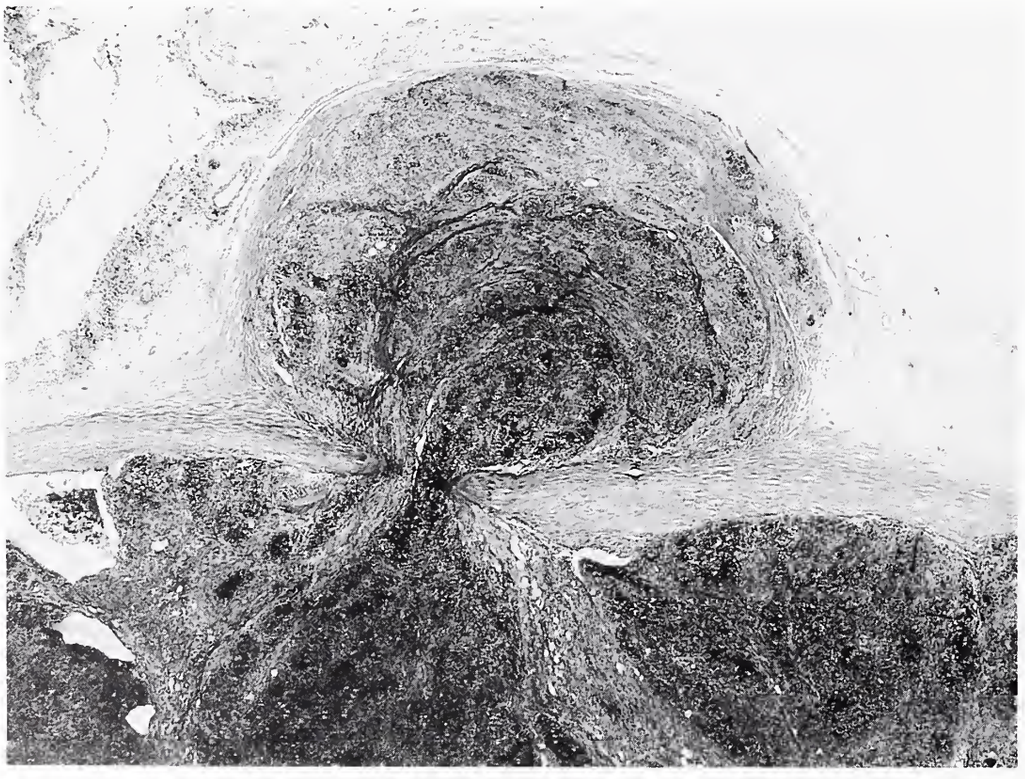


Figure 3-34
THYMOMA SHOWING CAPSULAR INVASION

A round tumor formed outside the capsule is also encapsulated.

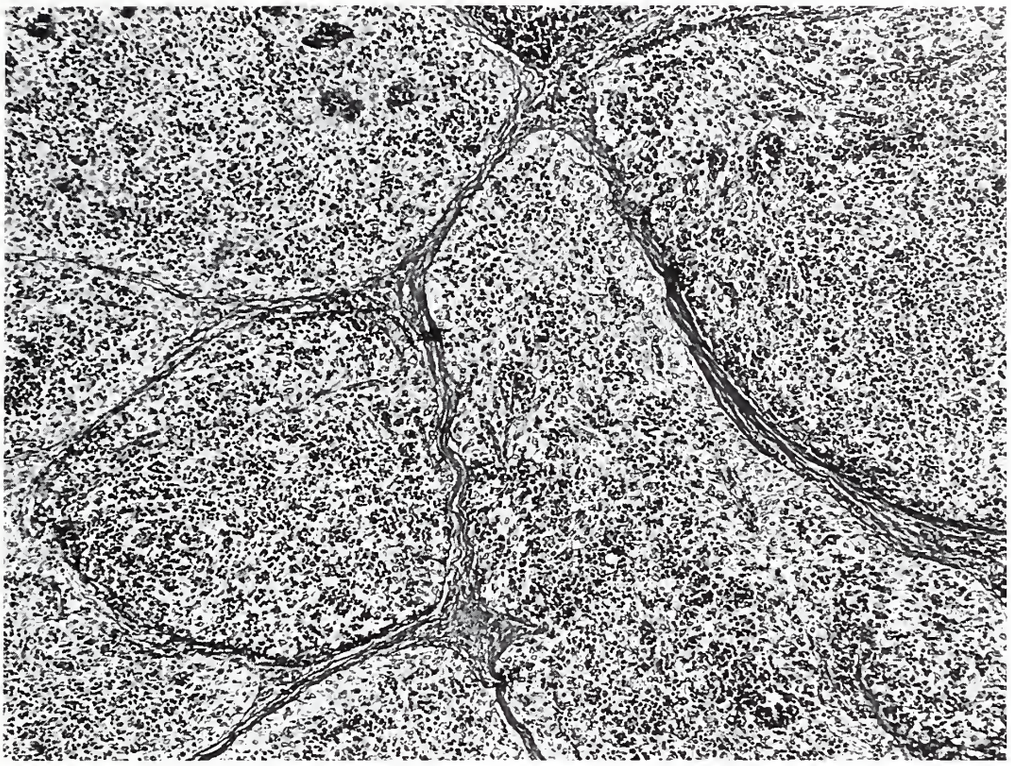


Figure 3-35
THYMOMA (MIXED LYMPHOCYTIC AND EPITHELIAL)
The tumor shows distinct lobulation due to bands of collagenous tissue.

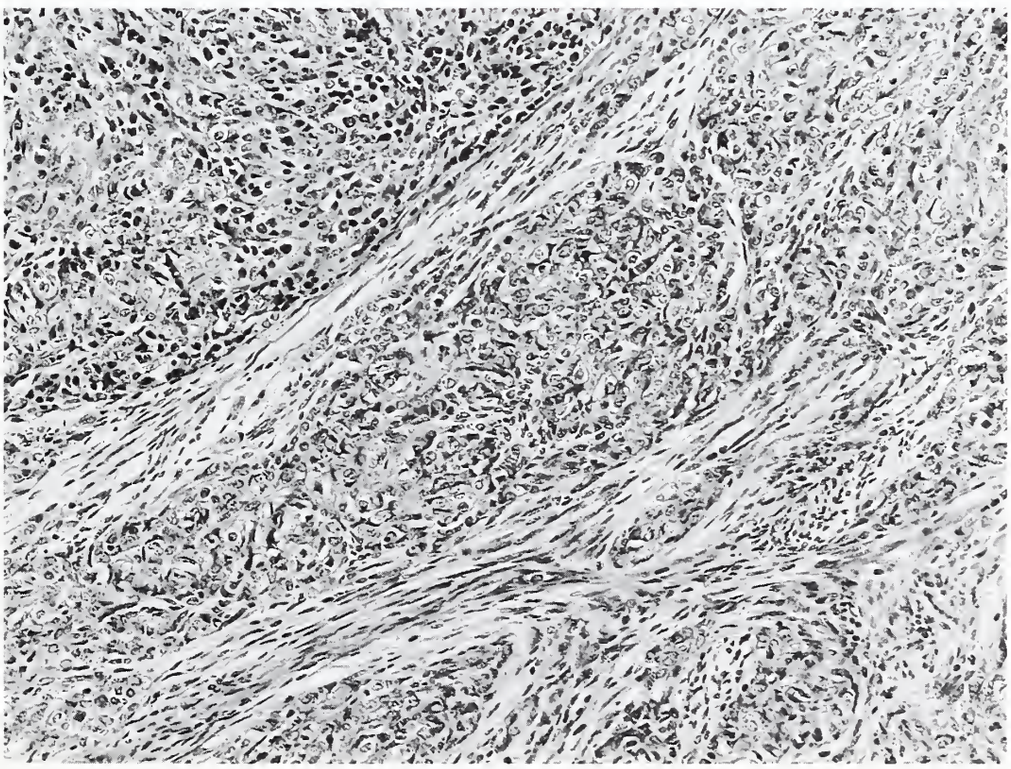


Figure 3-36
THYMOMA OF PREDOMINANTLY EPITHELIAL CELL TYPE (MIXED POLYGONAL AND SPINDLE CELL TYPE)
The tumor is subdivided into lobules consisting of polygonal tumor cells by bands of fibroblast-like spindle-shaped tumor cells.

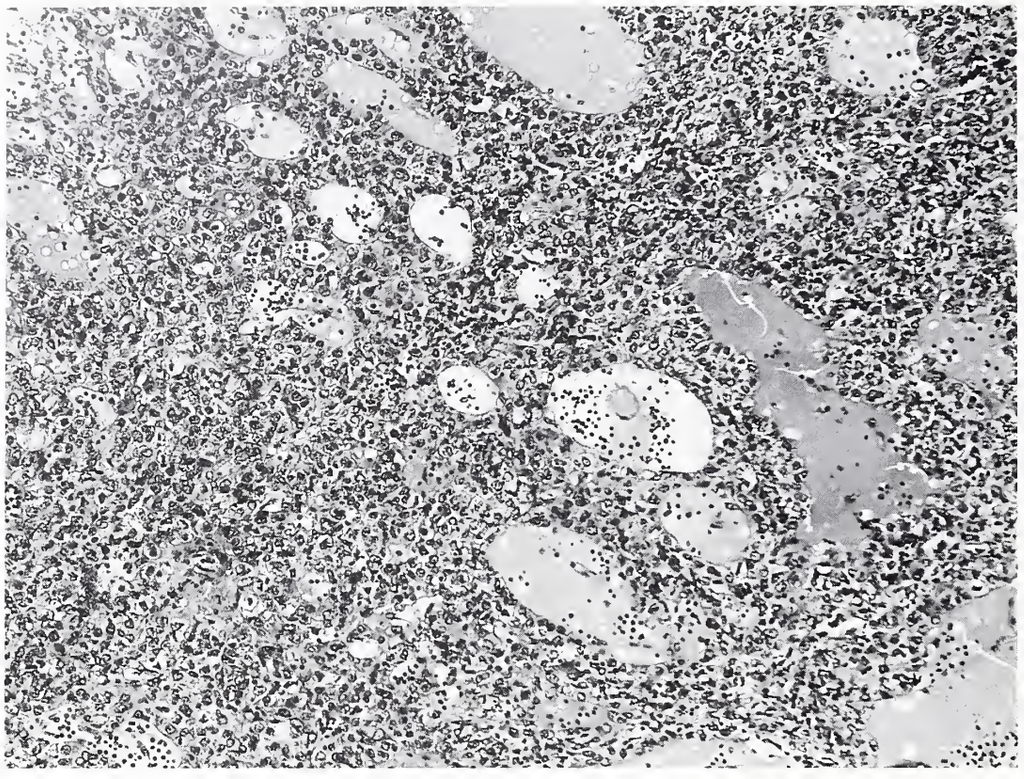


Figure 3-37
PERIVASCULAR SPACES IN THYMOMA

There are many small to medium-sized perivascular spaces in this predominantly epithelial, polygonal cell type thymoma. The spaces contain a central fine blood vessel, lymphoid cells, and serous fluid, and are lined by cuboidal epithelial cells.

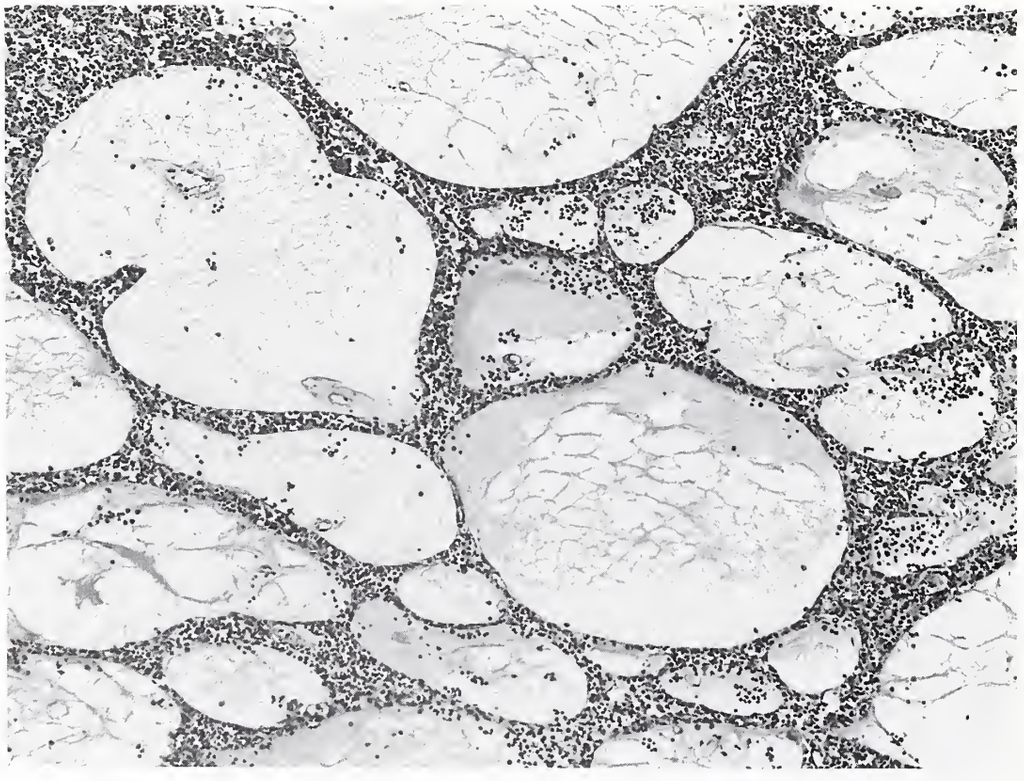


Figure 3-38
PERIVASCULAR SPACES IN THYMOMA

The perivascular spaces are cystically dilated and lined by inconspicuous epithelial cells. Central blood vessels may be difficult to find.

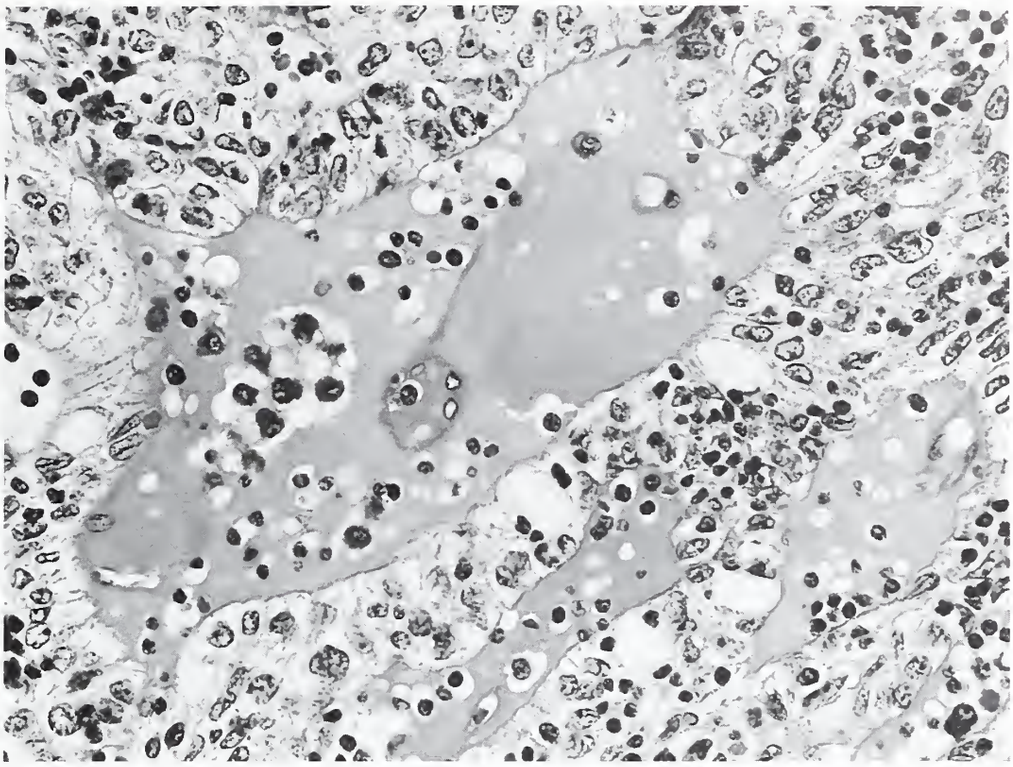


Figure 3-39
PERIVASCULAR SPACES IN THYMOMA
The perivascular spaces contain not only lymphoid cells and serous fluid but also mast cells. The lining epithelial cells are columnar with basal lamina.

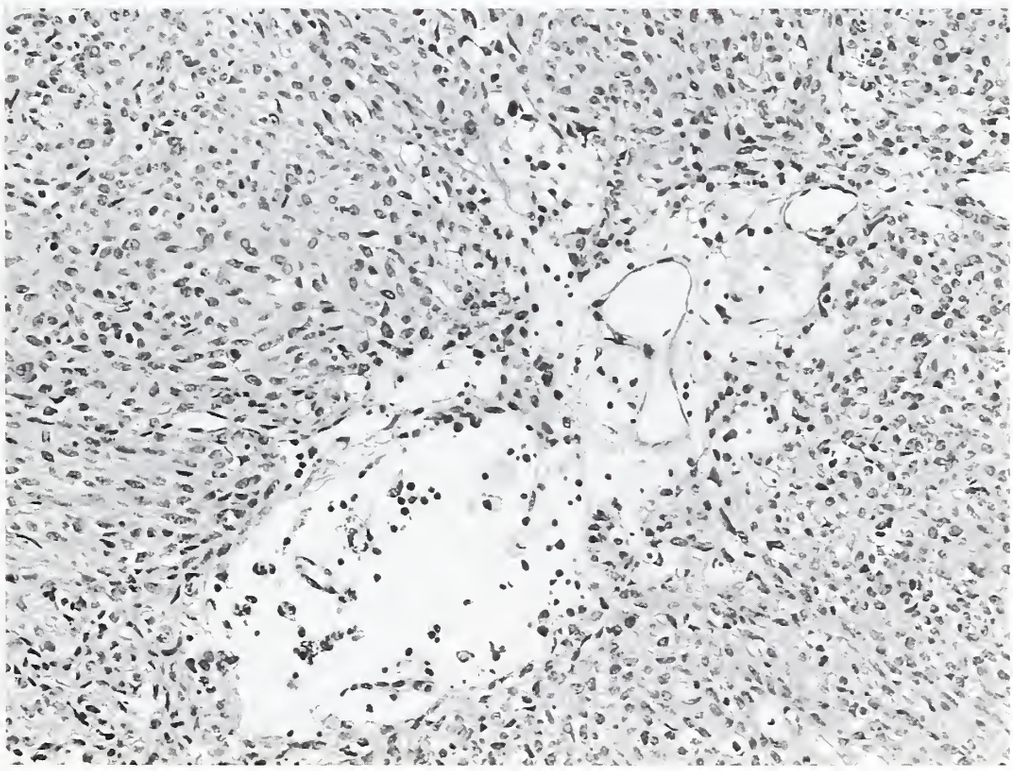


Figure 3-40
PERIVASCULAR SPACE IN THYMOMA
A perivascular space shows features of early organization with the appearance of fibroblasts.

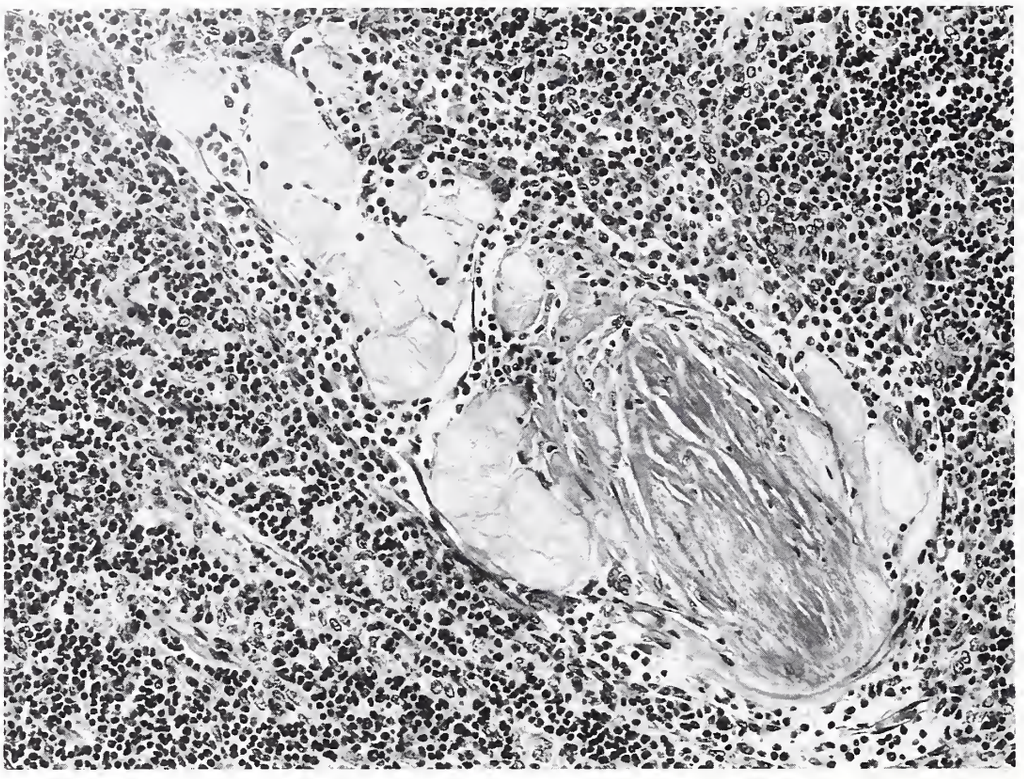


Figure 3-41
PERIVASCULAR SPACE IN THYMOMA
A perivascular space is being obliterated by fibrinous material and collagen.

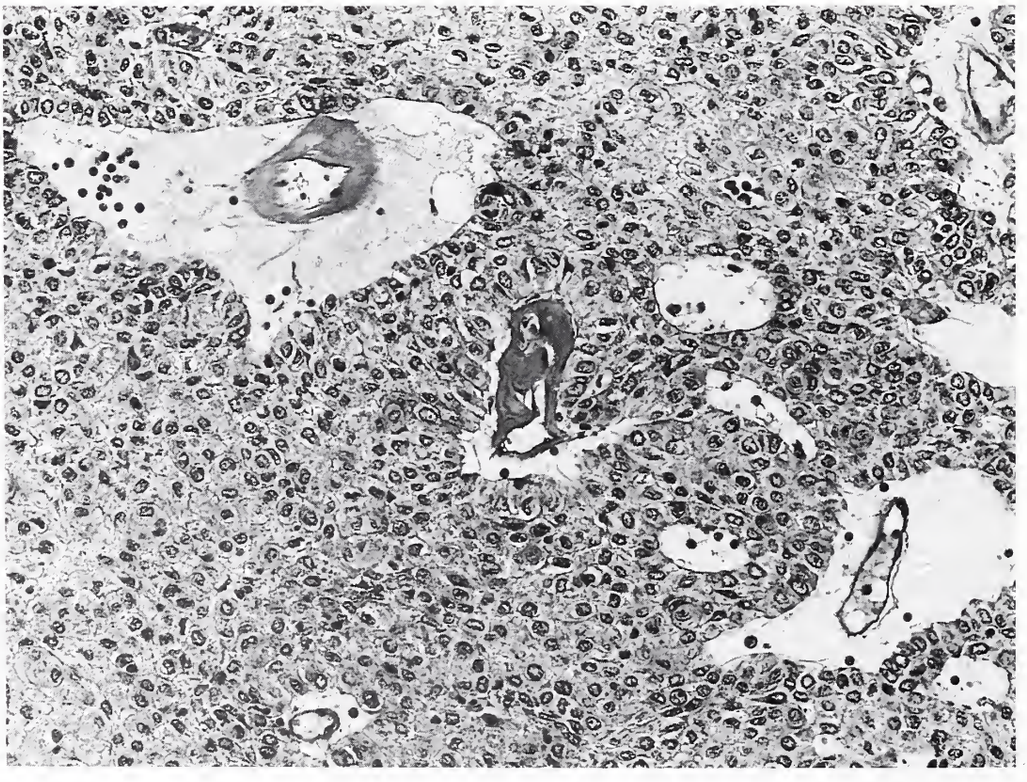


Figure 3-42
PERIVASCULAR SPACES IN THYMOMA
The walls of central blood vessels are hyalinized. The tumor is predominantly epithelial (polygonal cell type) with an epidermoid arrangement.

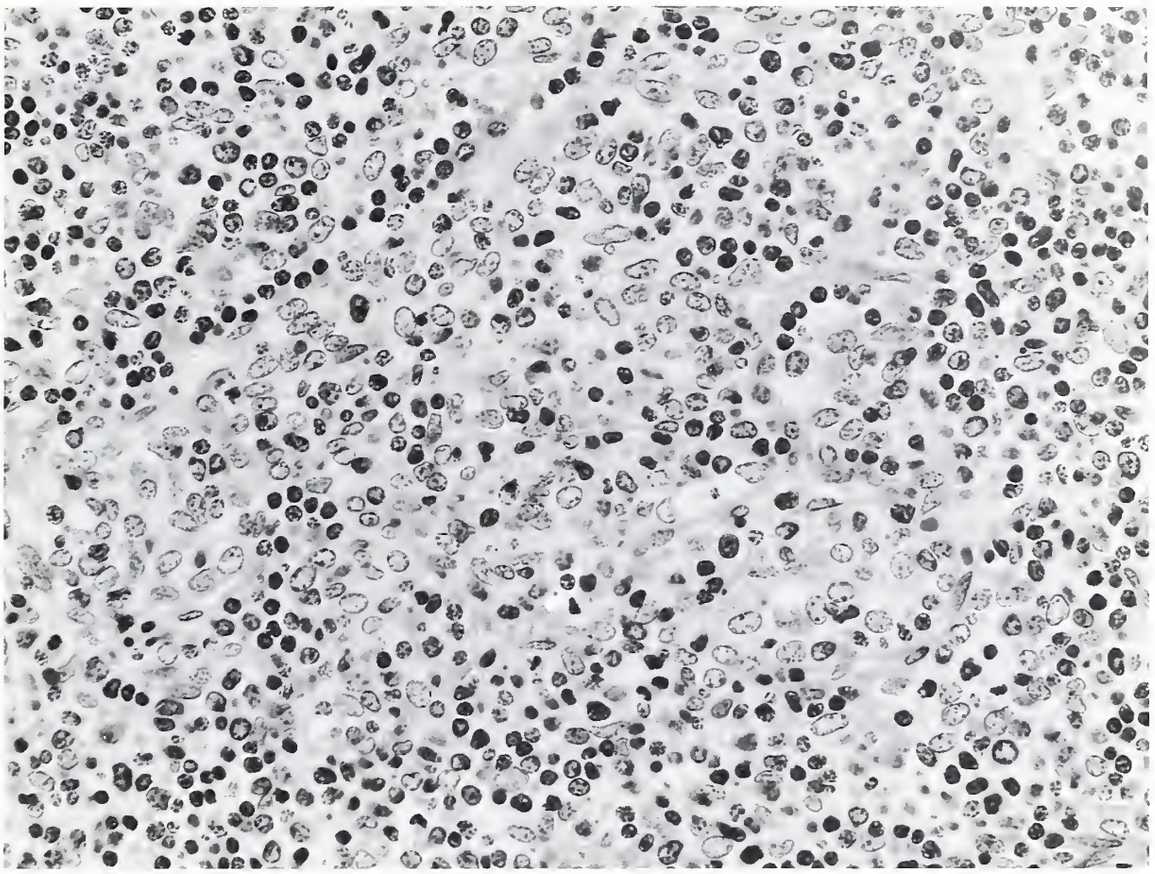


Figure 3-43
THYMOMA WITH POLYGONAL (OVAL) EPITHELIAL CELLS
Epithelial cells are rather small, with oval nuclei showing a fine chromatin pattern, inconspicuous nucleoli, scanty cytoplasm, and ill-defined cell borders.

former. In the spindle cell type, palisading of epithelial cells is not apparent. However, spaces are hardly seen in pure epithelial type thymoma, particularly the spindle cell type, although the reason for this is not clear. The presence of perivascular spaces in a mediastinal tumor is strongly suggestive of thymoma, particularly of the predominantly lymphocytic and mixed lymphocytic and epithelial types, and is an important feature for excluding the alternative diagnosis of malignant lymphoma. However, it is not a specific feature for thymoma, and may be seen in thymic carcinoma, although rarely (see Thymic Carcinoma). Structures similar to perivascular spaces in thymoma can also be seen in thymic carcinoid tumor, but most are simply artifacts since they are empty and do not contain either plasma or lymphocytes. Perivascular spaces were at one time considered to be perivascular lymphatic spaces, but endothelial cells cannot be identified.

Thymoma is composed of a mixture of neoplastic epithelial cells and non-neoplastic lymphocytes in varying proportions (51). At one end of the spectrum, the tumor appears to consist almost entirely of lymphocytes, mimicking diffuse malignant lymphoma; at the other, it is made up of a diffuse growth of polygonal epithelial cells or haphazardly arranged short spindle epithelial cells, which may create difficulties in the distinction from thymic carcinoma, localized fibrous tumor of the pleura (so-called fibrous mesothelioma), and other benign mesenchymal tumors. Between these two extremes is mixed epithelial and lymphocytic thymoma.

Subtyping of Thymoma by Epithelial Cell Type. The epithelial cells of thymoma vary in shape and size, but they have been customarily divided into polygonal (round or oval) (figs. 3-43–3-47) and spindle shaped (figs. 3-48–3-50). Recently, they have been divided into cortical and medullary types (70). Elongated spindle-shaped

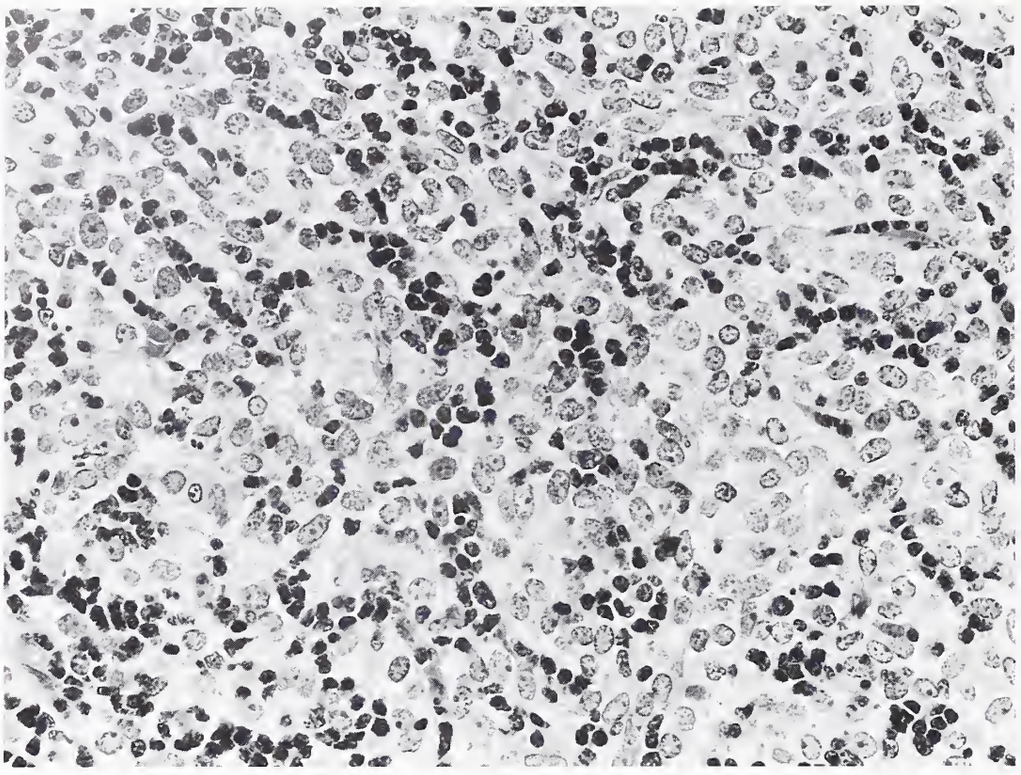


Figure 3-44
THYMOMA WITH POLYGONAL (OVAL) EPITHELIAL CELLS
Epithelial cells are medium-sized, with oval nuclei, a thin nuclear membrane, a fine chromatin pattern, some small nucleoli, and pale-staining cytoplasm.

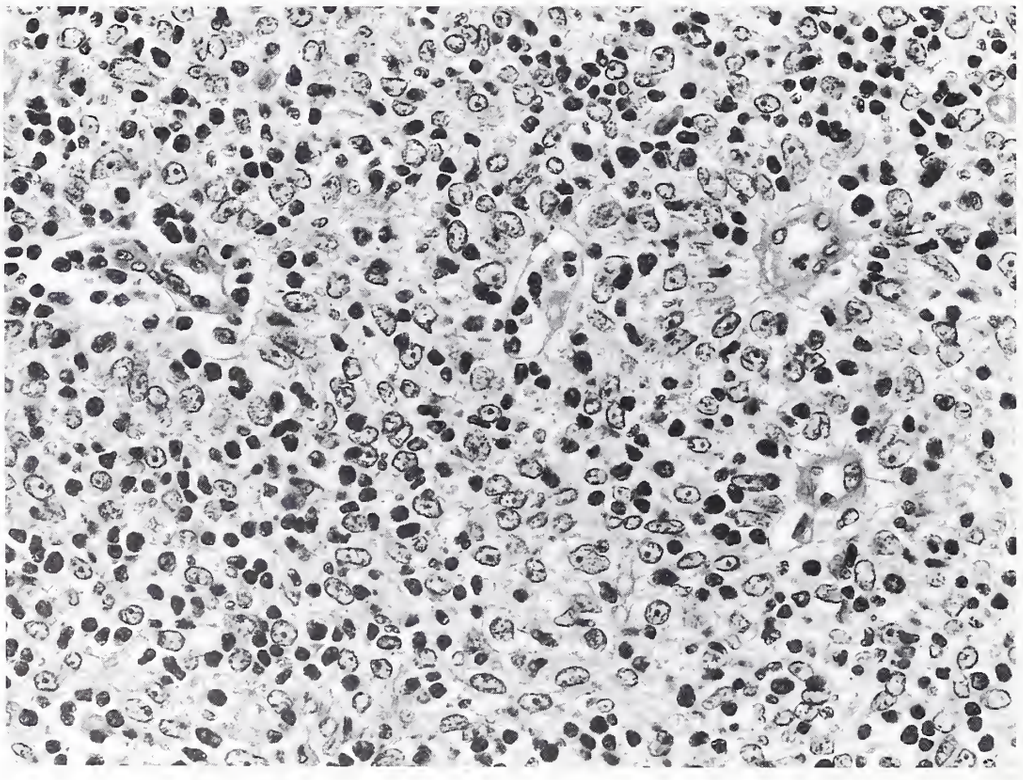


Figure 3-45
THYMOMA WITH POLYGONAL (OVAL) EPITHELIAL CELLS
Epithelial cells are medium-sized and have oval vesicular nuclei and moderately prominent nucleoli.

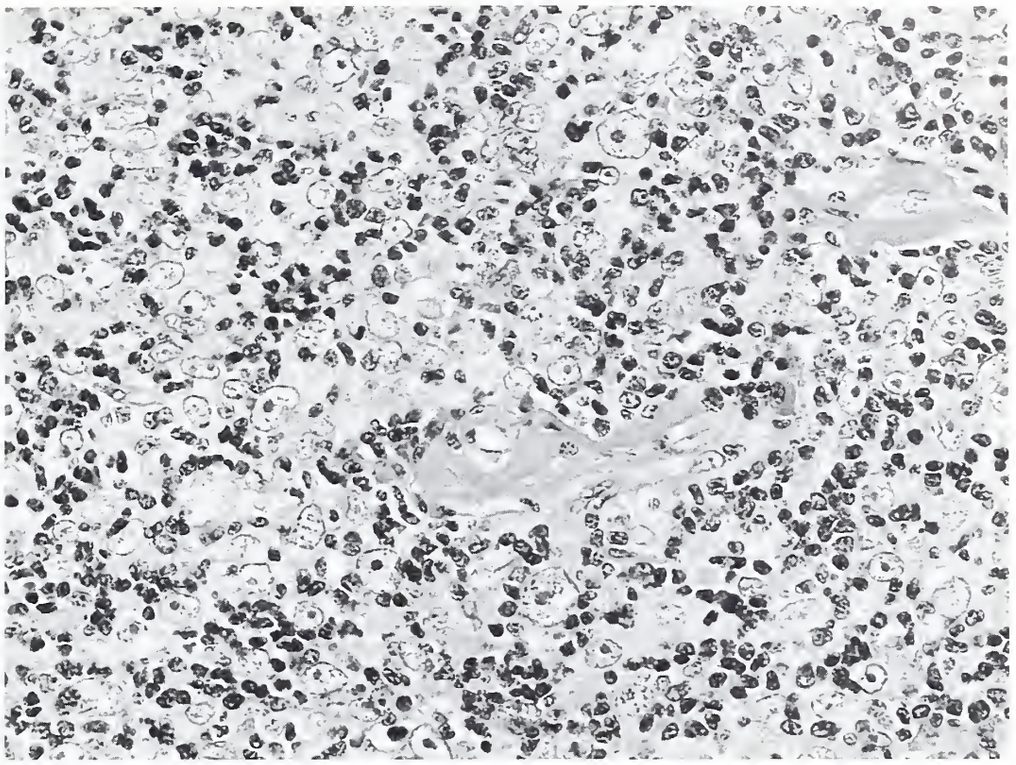


Figure 3-46
THYMOMA WITH POLYGONAL (OVAL) EPITHELIAL CELLS

The epithelial cells are moderately atypical and large, with large vesicular clear nuclei and prominent round nucleoli. Mitotic figures are rarely seen.

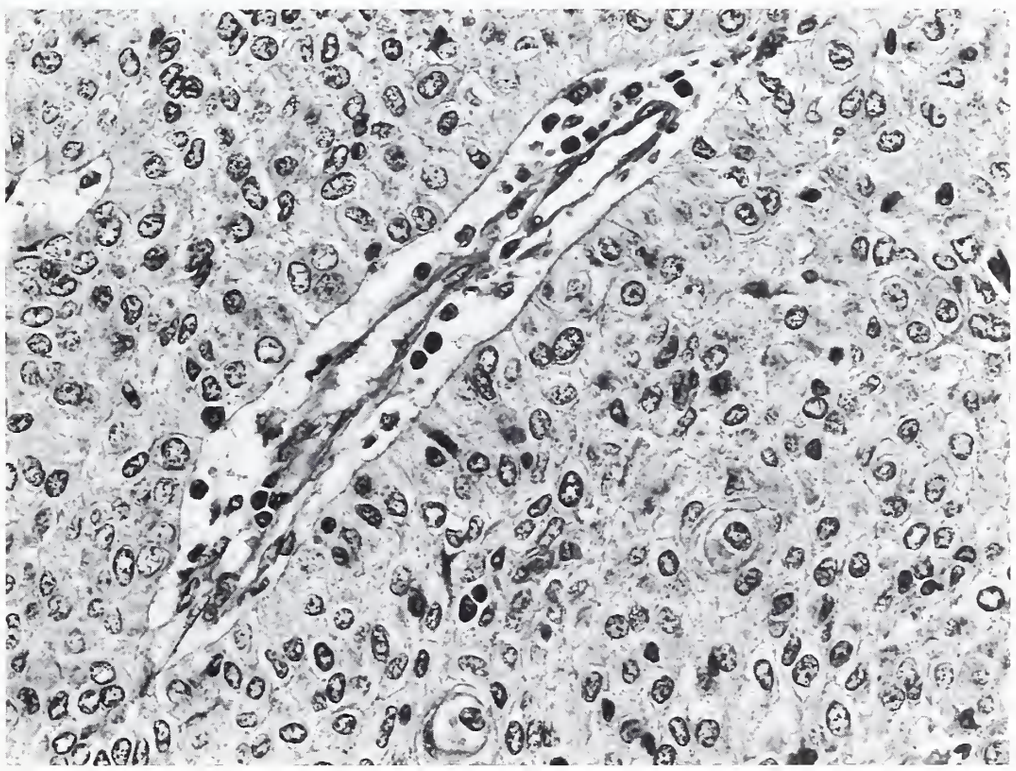


Figure 3-47
THYMOMA WITH POLYGONAL (OVAL) EPITHELIAL CELLS WITH ATYPIA AND AN EPIDERMOID ARRANGEMENT

The epithelial cells are moderately large, with hyperchromatic vesicular nuclei and some distinct nucleoli. They are arranged in whorls at a few points and in palisades around the perivascular space (same case as that in figure 3-31).

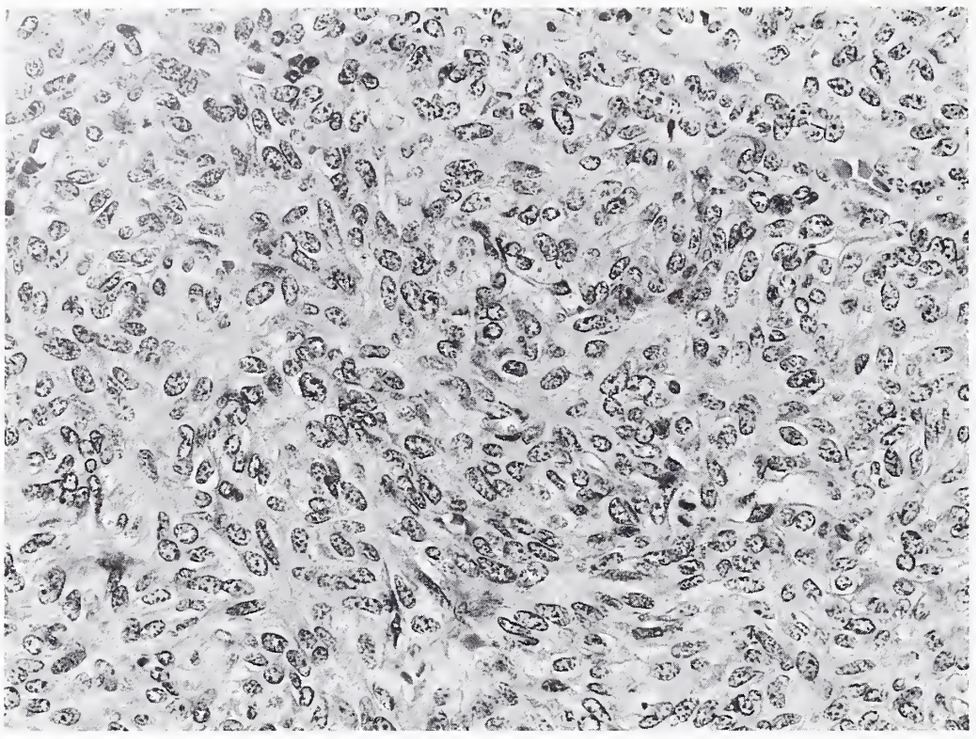


Figure 3-48
THYMOMA OF THE SPINDLE CELL TYPE

The epithelial cells are of the short spindle type with oval to elongated nuclei, granular chromatin, and inconspicuous nucleoli. The cells are arranged in irregular ill-defined bundles. The tumor somewhat resembles mesenchymal tumor or monophasic fibrous mesothelioma (same case as that in figure 3-18).

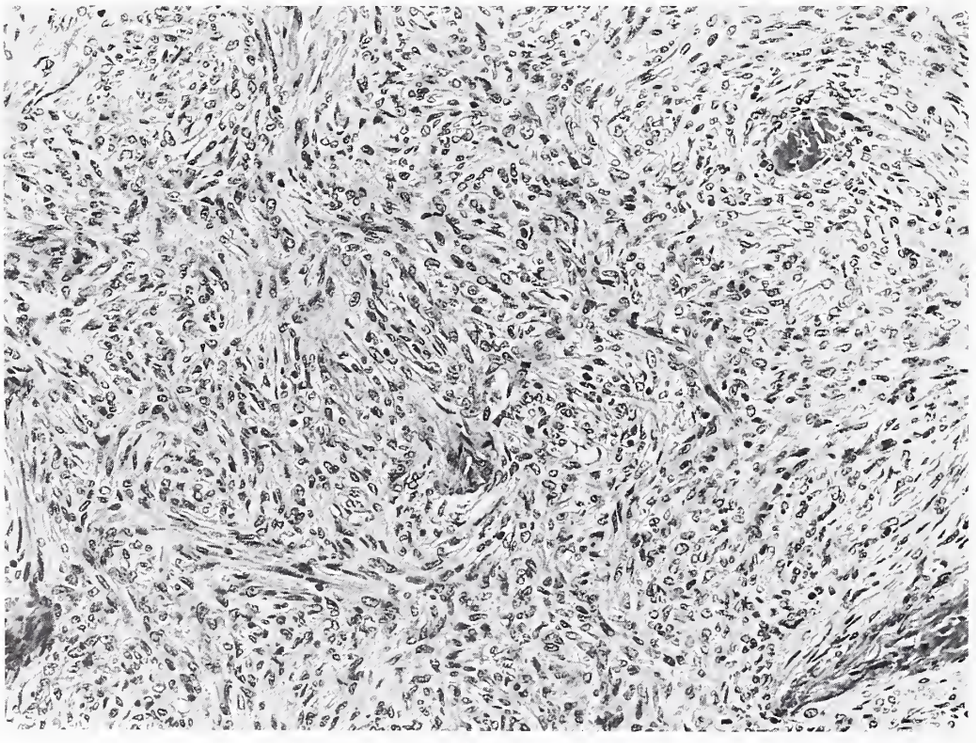


Figure 3-49
THYMOMA OF THE SPINDLE CELL TYPE

Fibroblast-like spindle cells show a storiform pattern. Although this resembles benign mesenchymal tumor, a few spindle tumor cells contain cytokeratin, and bundles of collagen are noted within the tumor, which are probably parts of the stroma subdividing the tumor into lobules.

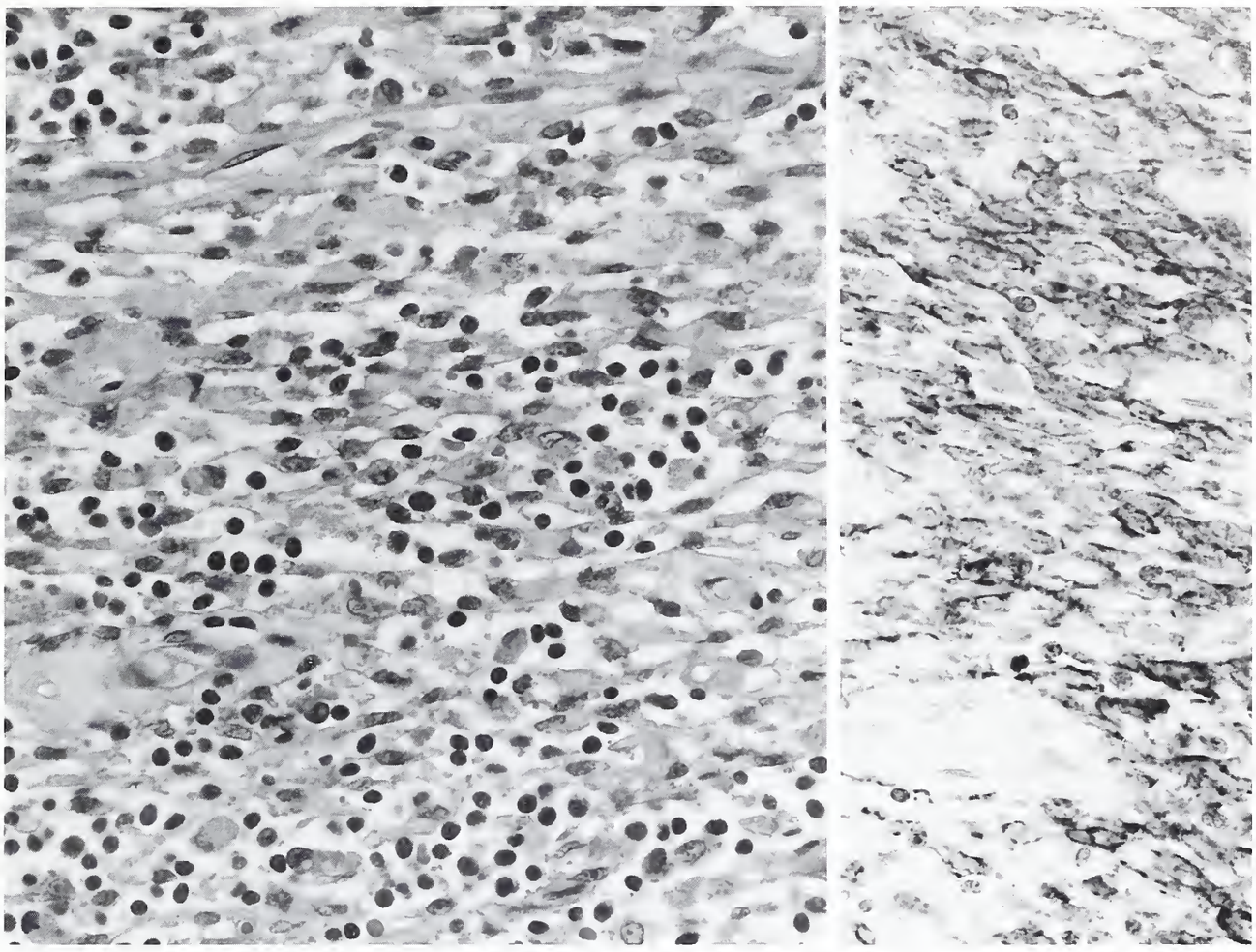


Figure 3-50
THYMOMA OF THE SPINDLE CELL TYPE

Left: Loosely arranged spindle cells resembling mesenchymal cells are diffusely infiltrated by lymphocytes.

Right: Immunostaining for cytokeratin discloses a positive reaction in the cytoplasm of almost all the tumor cells, indicating their epithelial nature.

cells may resemble fibroblasts, but their epithelial nature is supported by positive cytokeratin immunostaining (fig. 3-50). The separation of thymomas into polygonal (round or oval) cell type, mixed polygonal and spindle cell type, and spindle cell type may be difficult, due partly to the presence of intermediate categories. In our series of 73 thymomas, 52.1 percent were of the polygonal cell type, 31.5 percent of the mixed cell type, and 16.4 percent of the spindle cell type (56); the incidence of the spindle cell type is much higher than reported in other studies, but lower than the 22 percent in Taiwan reported by Pan et al. (84). The higher incidence of the spindle cell type thymoma may be partly due to the lower incidence of thymoma associated with myasthenia gravis in a cancer hospital, or to a geographic or ethnic factor.

The cortical type epithelial cells of Müller-Hermelink and associates (70,80,81), which are almost synonymous with the polygonal (round or oval) cell type, are characterized by a stellate outline with large, clear, round-oval nuclei and conspicuous nucleoli, and long prominent cellular processes (figs. 3-45, 3-46). However, cortical type epithelial cells may be medium-sized, with normochromatic bland nuclei, small nucleoli, and indistinct cytoplasmic processes (figs. 3-43, 3-44).

Medullary type epithelial cells correspond roughly to the spindle cell type with fusiform nuclei having dispersed or coarser chromatin, inconspicuous nucleoli, scant eosinophilic cytoplasm, and thin cellular processes (figs. 3-48–3-50). Occasionally, however, medullary type epithelial cells possess round to oval but bland nuclei, and may be arranged in several patterns

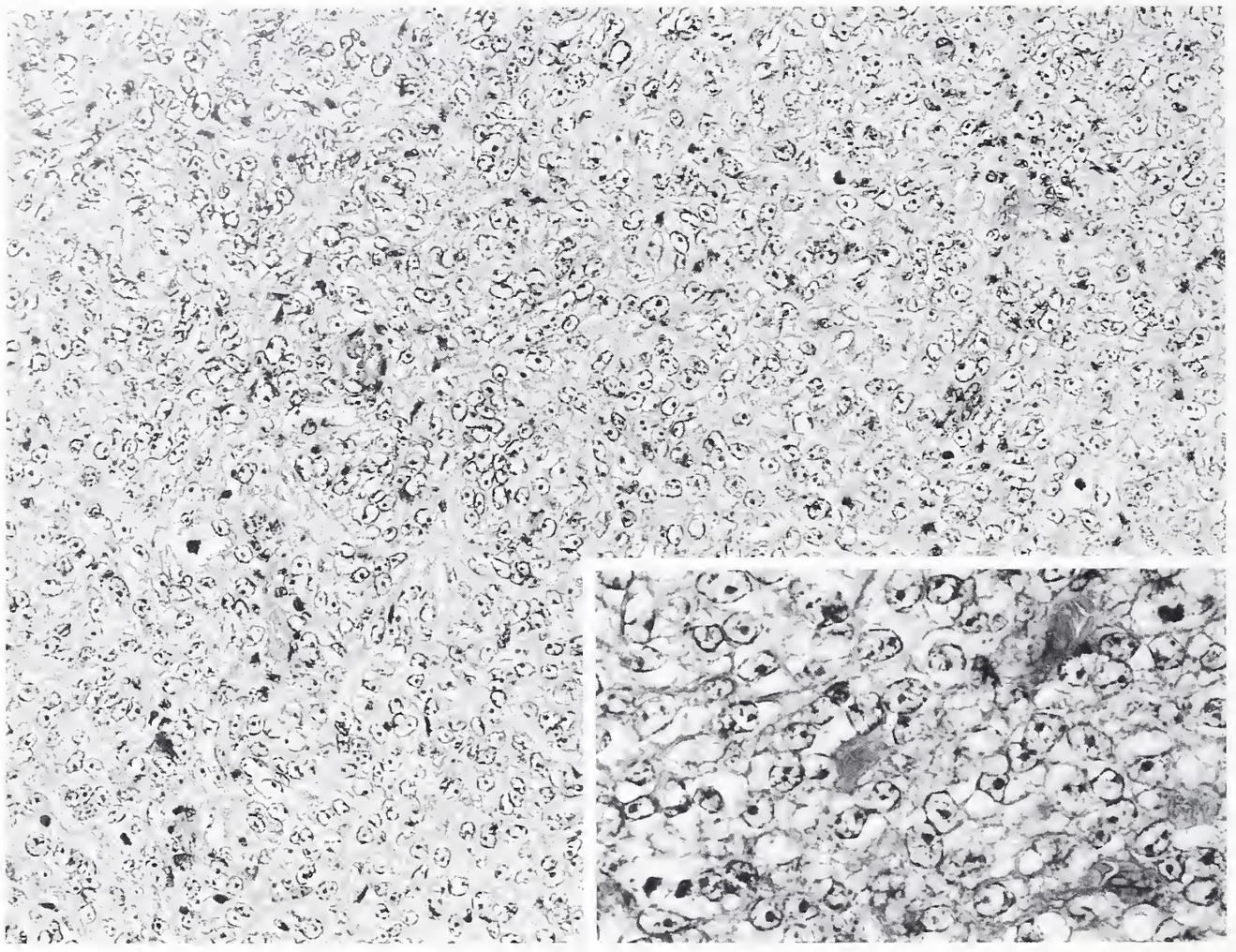


Figure 3-51
ATYPICAL THYMOMA WITH INCREASED MITOTIC ACTIVITY
In this field there is diffuse growth of polygonal cells with vesicular nuclei, prominent nucleoli, and at least two mitotic figures.

(discussed later). Squamous differentiation and Hassall corpuscles are rarely seen.

Spindle cell thymoma tends to remain localized to the anterior mediastinum. In contrast, the majority of thymomas invading neighboring organs or presenting with metastases are of the polygonal or mixed cell type. Mitotic figures may be seen in the polygonal cell type, but are rare in the spindle cell type; their frequency appears to be increased in tumors with increased nuclear atypia and nucleolar prominence (atypical thymoma). Mitotic figures are few and often difficult to find in most thymomas, but are increased up to 10 per 10 high-power fields in aggressive invasive thymomas of the polygonal cell type (fig. 3-51). Division of thymoma into polygonal and spindle-shaped epithelial cell types is important and useful because of their differences in aggressiveness (68). Table 3-4 lists the disease stages and patient prognosis for thymomas of various cell and histologic types. There is a higher frequency of earlier stages and a far better prognosis for patients with the spindle cell type than for those with the polygonal cell type.

The nuclei of the epithelial cells may be large and bizarre. Such a nuclear configuration not associated with mitotic activity is often found in patients with a history of radiotherapy (fig. 3-52). Therefore, it is most likely due to a degenerative process, and in fact may be present in untreated tumors showing degeneration.

The lymphocytes accompanying thymoma are non-neoplastic (51), usually with small dark-stained nuclei and an almost invisible cytoplasm. Occasionally, they have an "active" appearance: increased size, a recognizable chromatin pattern,

Table 3-4

MODIFIED CLINICAL STAGE DISTRIBUTION AND OUTCOME OF THYMOMA BY HISTOLOGIC AND CYTOLOGIC SUBTYPES*

	Stage I	Stage II	Stage III	Stage IV†	Total
Histologic subtype					
Predominantly lymphocytic	14 (45.2)**	12 (38.7)‡	4 (12.9)	1 (3.2)	31
Mixed lymphoepithelial	12 (37.5)	9 (28.1)§	7 (21.9)‡#	4 (12.5)§	32
Predominantly epithelial	3 (30.0)‡	2 (20.0)	1 (10.0)	4 (40.0)‡§	10
Epithelial cell subtype					
Polygonal	12 (31.6)	11 (28.9)§	7 (18.4)§	8 (21.1)¶	38
Mixed	9 (39.1)	9 (39.1)	4 (17.4)‡¶	1 (4.3)‡	23
Spindle	8 (66.7)‡	3 (25.0)	1 (8.3)	0 (0.0)	12
Total	29	23	12	9	73

*National Cancer Center Hospital, Tokyo.
**Parentheses indicate percentage of each subtype by stage.
†Stage IV includes one case with pulmonary metastasis, one case with lymph node metastasis, and the remaining seven cases with pleural dissemination.
‡One patient alive with recurrent tumor.
§One case of tumor death.
¶Two cases of tumor death.
#Three cases of tumor death.

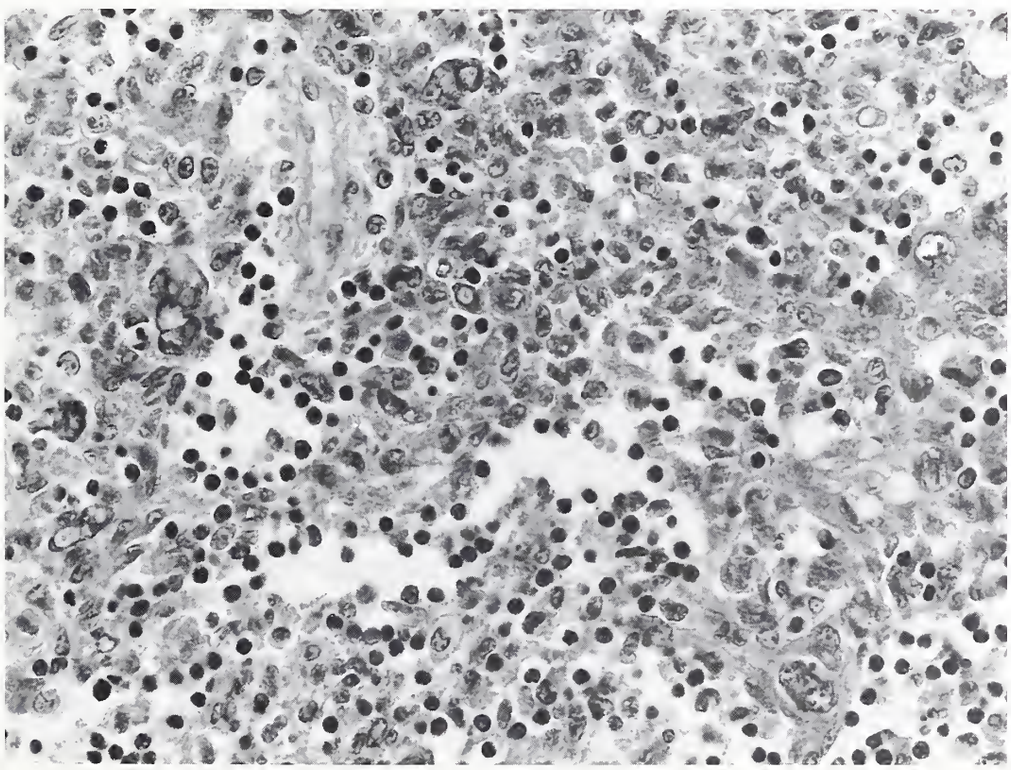


Figure 3-52
THYMOMA WITH GIANT EPITHELIAL CELLS

Scattered in mixed lymphocytic and epithelial type thymoma are uni- and multinucleated giant epithelial cells and epithelial cells with vacuolated nuclei. These nuclear changes are considered to be due to irradiation and chemotherapy instituted before death (autopsy case).

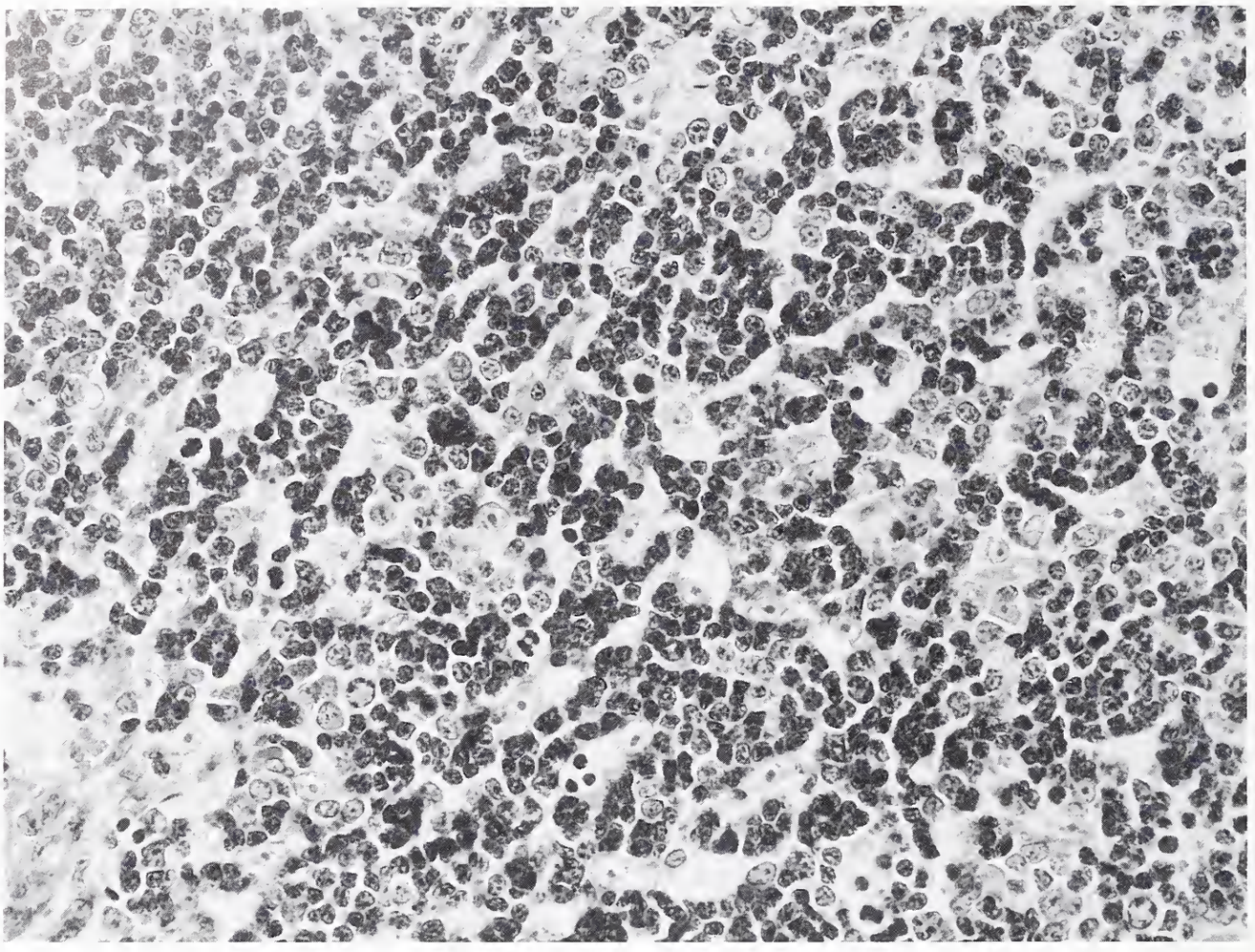


Figure 3-53
LYMPHOCYTE PREDOMINANT THYMOMA

Many lymphocytes are active and large, with a recognizable nuclear chromatin pattern and small nucleoli. Several mitotic figures are seen. Epithelial cells are polygonal with clear nuclei and distinct nucleoli.

a cytoplasmic rim, and mitotic activity (fig. 3-53). Whether the cells undergoing mitosis are epithelial cells or lymphocytes can be distinguished roughly by the cell size and by immunostaining for cytokeratin and surface markers of lymphocytes. Lymphocytes associated with medullary type epithelial cells are largely mature and small, and those associated with cortical type epithelial cells are of both mature and immature types; the latter are medium sized with granular nuclei active in appearance.

Subtyping by Histology. As already described, thymoma is customarily divided into predominantly lymphocytic, mixed epithelial and lymphocytic, and predominantly epithelial types according to the amount of the predominating cell type, although defining "predominant" is often difficult and arbitrary. In our series of 73 cases, 42.5 percent were predominantly lymphocytic, 43.8 percent were mixed, and 13.7 percent were predominantly epithelial. There seems to be a tendency for the lymphocyte predominant and mixed types to decrease in frequency with advanced disease stage, whereas this is not the case for the predominantly epithelial cell type (Table 3-4). Morphologic subtyping of epithelial cells, therefore, must combine histologic subtyping based on the amount of lymphocytes and epithelial cells with epithelial cell subtyping for better assessment of clinical outcome (see Table 3-2).

Lymphocyte predominant thymoma should not be misinterpreted as malignant lymphoma. The most important distinguishing feature is the presence of scattered large cells with lightly stained nuclei in a diffuse lymphocytic background. These cell possess large, vesicular,

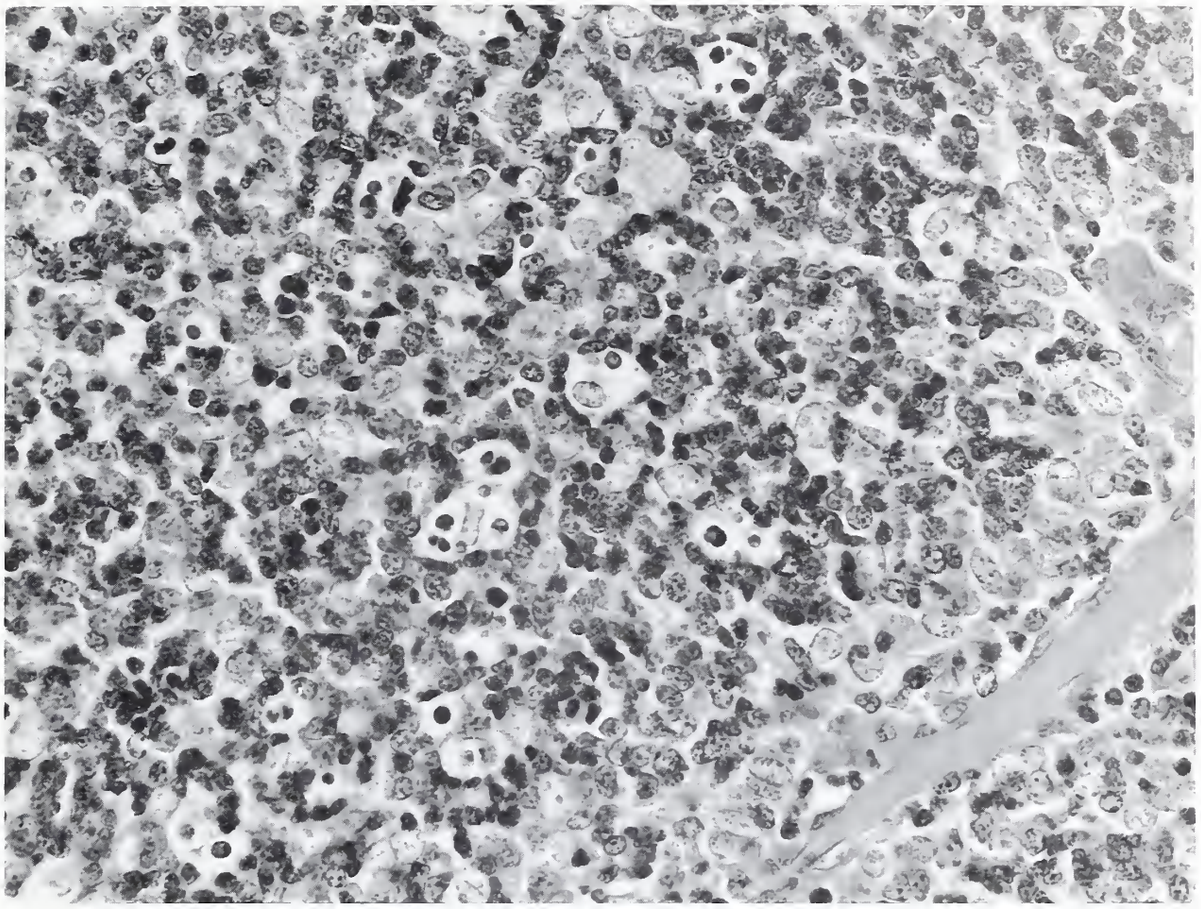


Figure 3-54
LYMPHOCYTE PREDOMINANT THYMOMA WITH STARRY SKY APPEARANCE
The scattered large clear cells within this lymphocyte-rich thymoma are macrophages, which contain a few lymphocytes with pyknotic nuclei.

round or indented nuclei; distinct nucleoli; and often clear cytoplasm. These are characteristic features of polygonal epithelial cells as compared with the darker, more condensed nuclei of lymphocytes (see fig. 3-11). For confirmation, immunostaining for cytokeratin makes the epithelial cells stand out among the nonstaining lymphocytes and macrophages (see fig. 3-76). Histiocytes scattered in the tumor may produce a starry sky appearance, which can be distinguished easily from epithelial cells by the presence of intracytoplasmic nuclear debris (fig. 3-54). This is never as prominent as that seen in Burkitt's lymphoma and undifferentiated lymphoblastic lymphoma of the T-cell type.

In thymomas of the lymphocyte predominant type and those with areas of lymphocyte predominance, there may be well-defined, round or slightly irregular zones with a clear and lighter-stained appearance than the surroundings; these have been interpreted as foci of medullary differentiation (figs. 3-11, 3-55). Superficially, they resemble germinal centers, but their clear appearance is due to lower numbers of lymphocytes than in their surroundings. Histologically, areas of medullary differentiation in thymoma resemble the medulla of the thymus, also because of the occasional epithelial cell aggregates similar to Hassall corpuscles (fig. 3-56). Immunohistochemically, the foci are composed of mature or medullary T cells, characterized by CD1a-, CD3+, and CD4+ or CD8+ phenotypes (see fig. 3-83) (98).

Mixed lymphocytic and epithelial thymomas can be diagnosed with relative ease: the epithelial cells and lymphocytes are intimately associated in most instances (see figs. 3-43, 3-46). In a single tumor, the proportions of epithelial cells and lymphocytes vary among the lobules; a lobule with mixed cellularity may be present adjacent to an epithelial cell predominant lobule, with fibrous

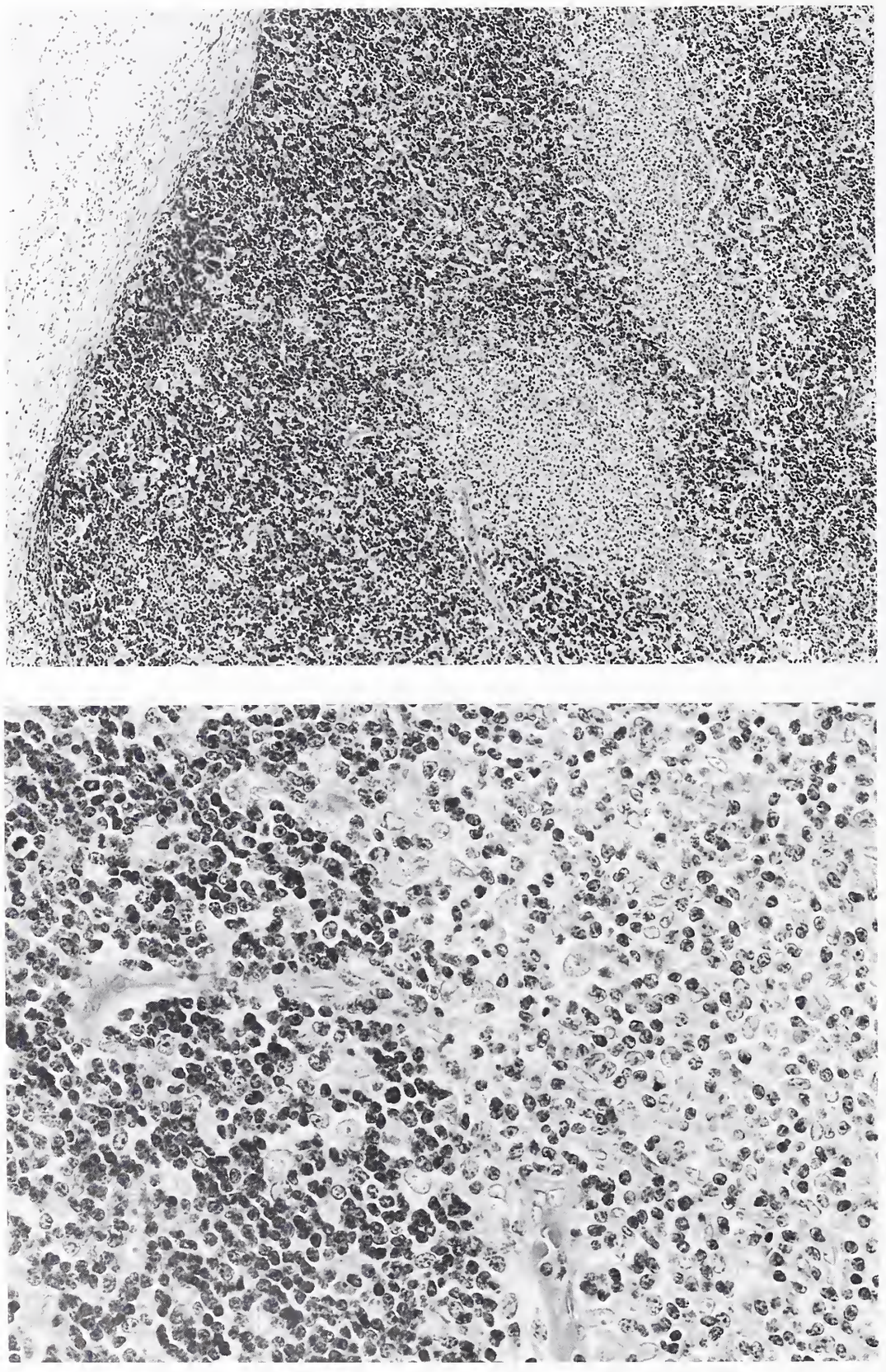


Figure 3-55

LYMPHOCYTE PREDOMINANT THYMOMA SHOWING MEDULLARY DIFFERENTIATION

Top: Tumor metastatic to the lung reveals two oval-shaped, fairly well-defined, lighter-stained areas of medullary differentiation, where lymphocytes are less densely packed.

Bottom: Higher magnification of the border of medullary differentiation discloses a different epithelial cell morphology, i.e., epithelial cells at the periphery of and in areas surrounding medullary differentiation are larger, with more prominent nucleoli than those in areas without medullary differentiation, where nucleoli are inconspicuous.

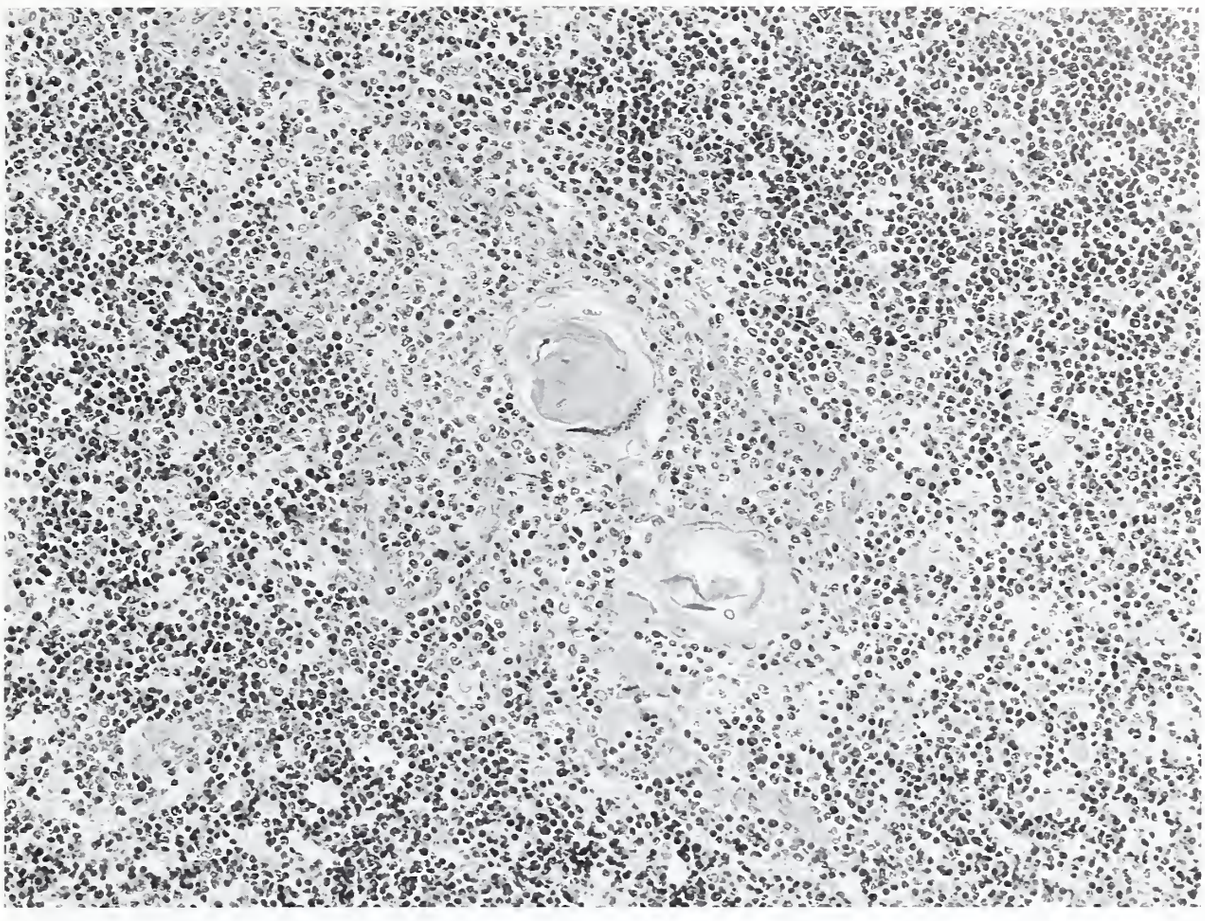


Figure 3-56
HASSALL CORPUSCLES IN LYMPHOCYTE PREDOMINANT THYMOMA
A focus of medullary differentiation with Hassall corpuscles, which looks like normal thymic tissue. Hassall corpuscles most likely represent differentiation in thymoma but inclusion of normal thymic tissue cannot be overlooked.

bands between them. Lobules are often clearly bordered by a rim of epithelial cells and supported by the fibrous bands, but lobules of predominantly lymphocytic or mixed cellularity may merge imperceptibly into areas composed of spindle-shaped, elongated epithelial cells and scanty lymphocytes (fig. 3-57).

Features that allow differentiation from lymphoepithelioma-like undifferentiated (or poorly differentiated squamous cell) carcinoma are marked atypia and anaplasia, together with increased mitotic activity in the individual carcinoma cells (see fig. 3-124). In addition, the phenotypes of the infiltrating lymphocytes are different. As described in the following chapters, immature (or cortical) T cells are almost always found in thymoma, but infiltrating lymphocytes in carcinoma possess mature T-cell phenotypes as well as B cells and plasma cells.

The histologic features of epithelial cell predominant thymoma vary greatly. Short spindle cells may be arranged haphazardly (reminiscent of those seen in benign localized fibrous tumor of the pleura) or elongated spindle cells may be arranged in a storiform pattern (resembling benign fibrous histiocytoma) (figs. 3-48–3-50). In such tumors, lymphocytes are scanty and may be hardly detectable.

Another relatively common form of epithelial cell predominant thymoma consists of sheets and lobules of polygonal cells with moderately large vesicular to hyperchromatic granular nuclei, small nucleoli, and a scant to moderate amount of cytoplasm (figs. 3-42, 3-47, 3-58, top). This tumor has an "epidermoid" appearance and probably coincides with the well-differentiated thymic carcinoma (an organotypical and low-grade malignant carcinoma) described by Kirchner and

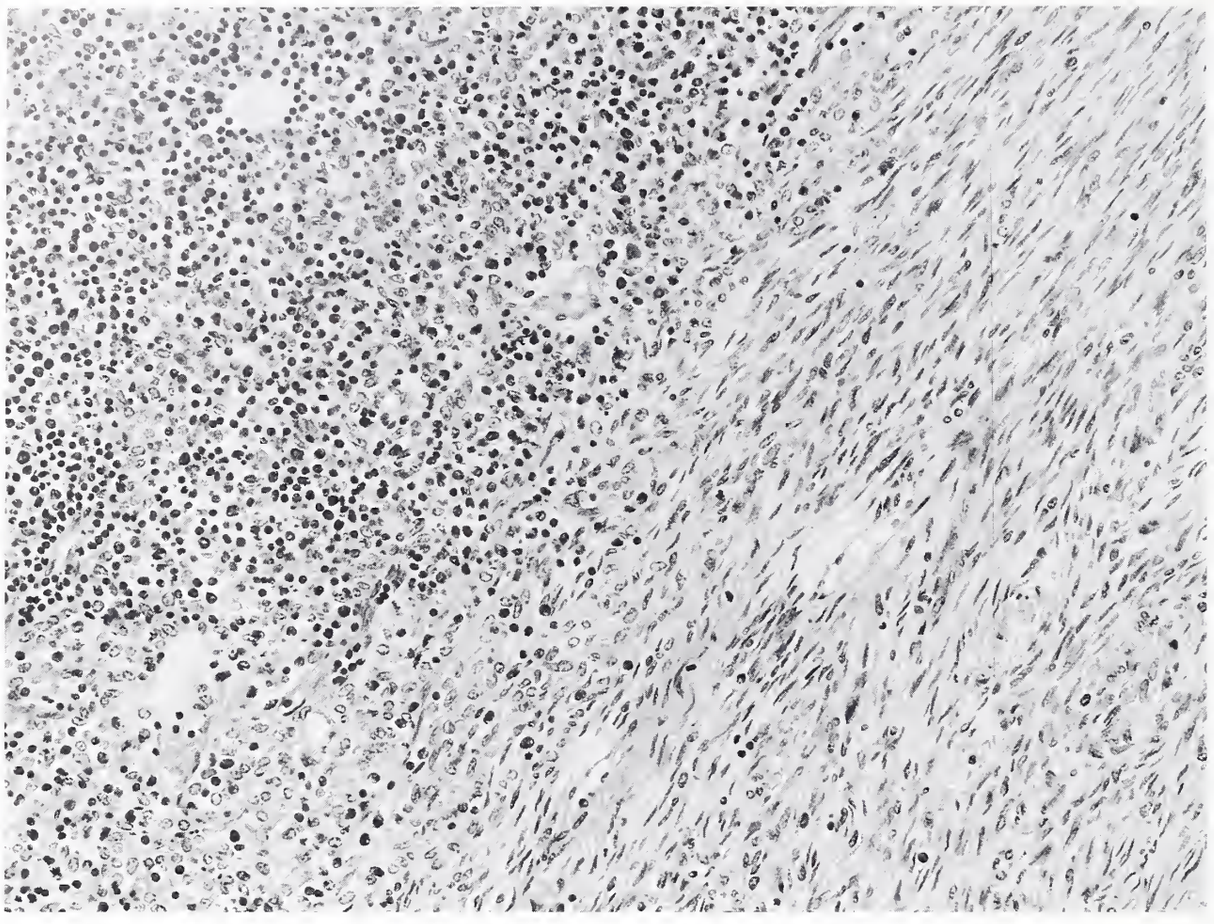


Figure 3-57
MIXED POLYGONAL AND SPINDLE CELL THYMOMA
An area composed of mixed lymphocytic and polygonal epithelial cell thymoma merges into an area consisting of predominantly epithelial spindle cell thymoma.

associates (53). They chose to call it carcinoma because it appears to be aggressive, with an increased number of mitotic figures and frequent invasion of surrounding organs or tissues. However, it still retains the organoid features of thymoma and attracts immature T cells. Furthermore, it is said to be often associated with myasthenia gravis. In contrast, a lack of immature T cells and no association with myasthenia gravis are noted in the tumor traditionally classified as thymic carcinoma (see Thymic Carcinoma).

Subtyping by Histogenesis. Müller-Hermelink and associates divided thymoma initially into four, and later into five, histologic subtypes (52,53,70), a practice that has been adopted by other investigators (47,61,86,89,90). These five subtypes are medullary thymoma, mixed medullary and cortical thymoma, predominantly cortical (organoid) thymoma, cortical thymoma, and well-differentiated thymic carcinoma (53,70,90).

Medullary thymoma is composed of medullary type epithelial cells with few or moderate numbers of mature lymphocytes. There may be a storiform pattern, hemangiopericytoma-like pattern, rosette-like structures, or even glandular formation of flat, cuboidal to cylindrical epithelial cells resulting in an adenoma-like pattern (figs. 3-48–3-50, 3-59–3-62, 3-78, 3-80). Microcystic and macrocystic changes may be seen (figs. 3-63–3-65). Since some medullary thymomas are composed of nonspindle cells, the term "spindle cell" cannot be used as a substitute for "medullary."

Mixed thymoma is composed of a mixture of medullary thymoma and cortical thymoma, and can be divided into three major patterns: 1) lobules of medullary type epithelial cells mixed with lymphocyte-rich lobules and cortical type epithelial cells; 2) nests of medullary type epithelial cells surrounded by sheets of lymphocyte-rich predominantly cortical components (figs. 3-36,

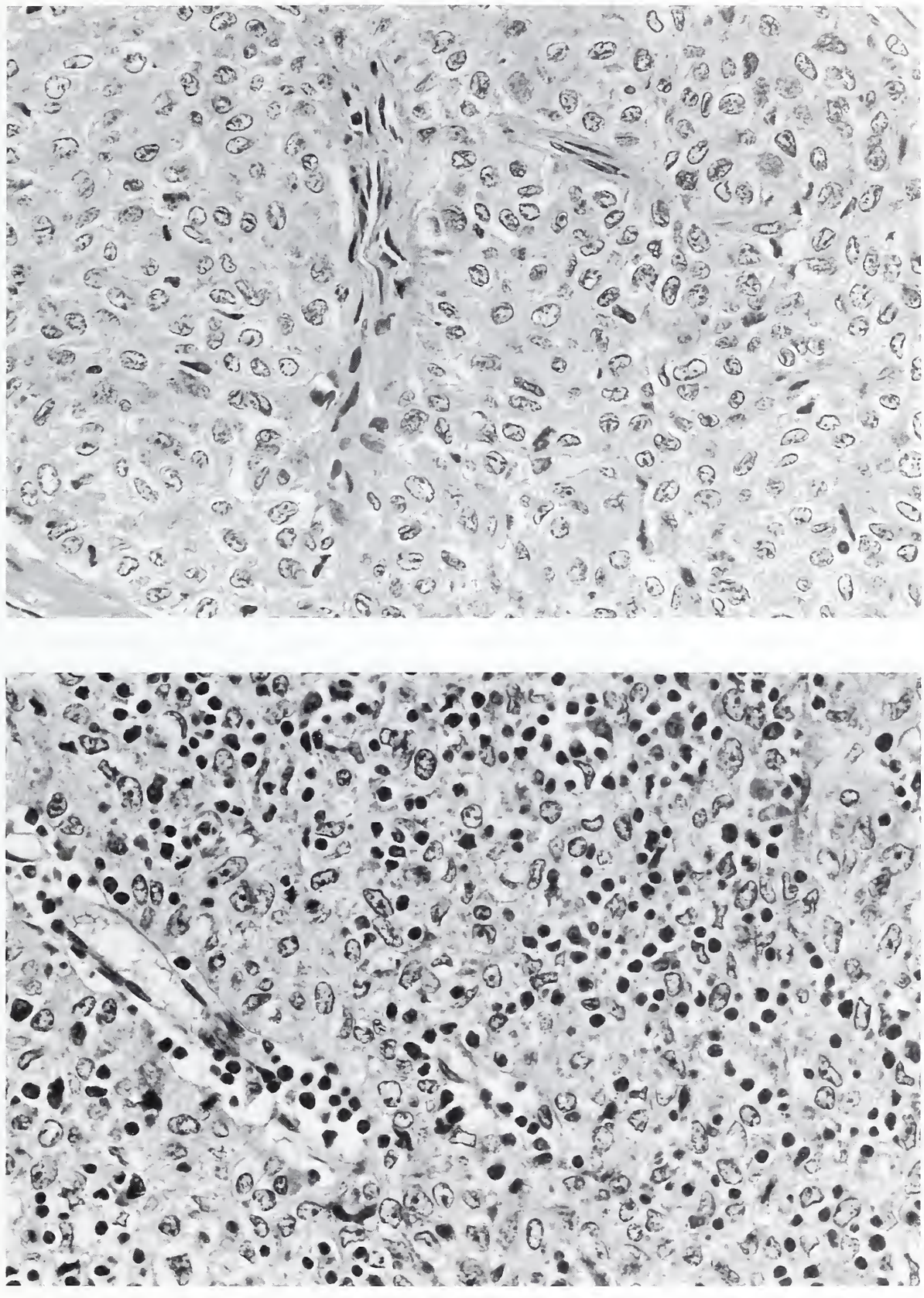


Figure 3-58

PREDOMINANTLY EPITHELIAL THYMOMA WITH CELLULAR ATYPIA (ATYPICAL THYMOMA)

Top: Metastasis in the liver consisting of diffuse growth of moderately pleomorphic polygonal cells with hyperchromatic nuclei and a moderate amount of cytoplasm.

Bottom: The primary tumor removed together with a pulmonary lobe 6 years prior to death reveals mixed cellularity of lymphocytes and polygonal epithelial cells and a small perivascular space.

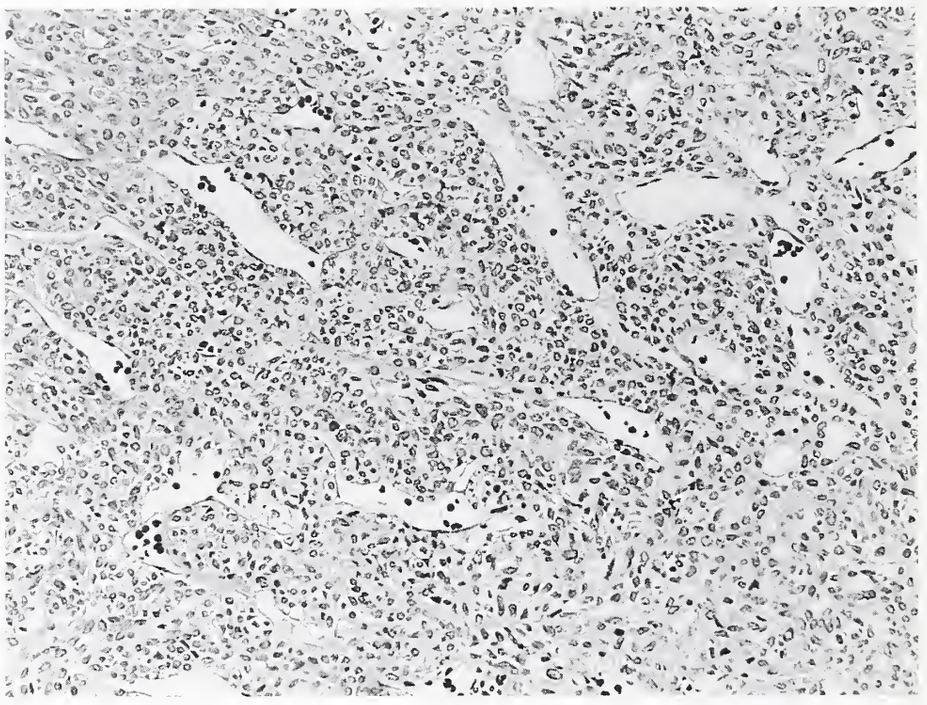


Figure 3-59
THYMOMA WITH HEMANGIO-PERICYTOMATOUS FEATURES

Diffuse growth of polygonal and short spindle cells is associated with dilated sinusoidal vasculature, reminiscent of hemangiopericytoma (same case as that in figure 3-63).

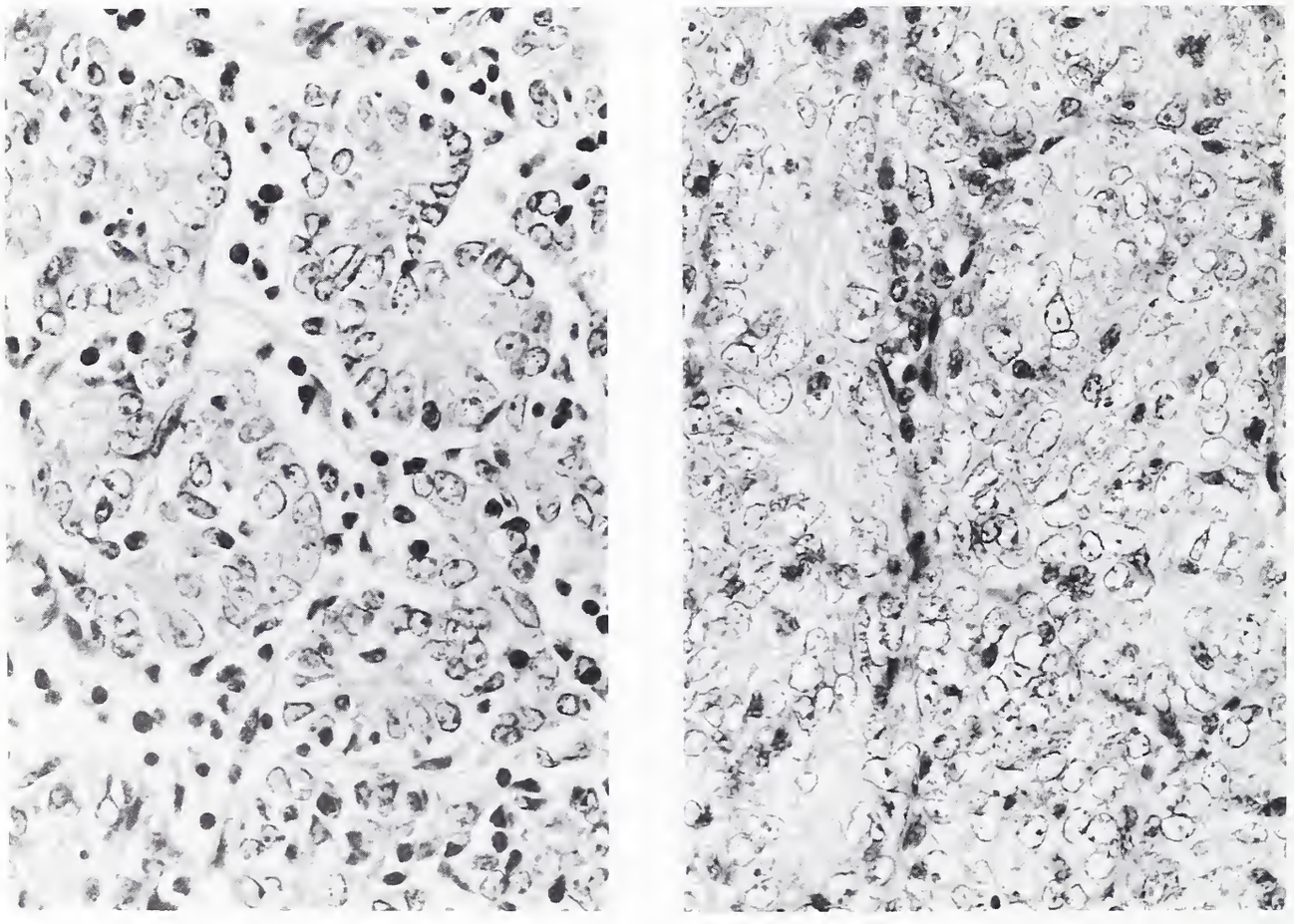


Figure 3-60
ROSETTE-FORMING THYMOMA

This tumor, metastatic to the lung, was found 3 years after surgical resection of thymoma. The pyramidal tumor cells with basal nuclei form rosettes without central lumina. The cells have a back-to-back arrangement with lymphocytic infiltration between.

Left: Artificial spaces between rosettes.

Right: Rosettes without artificial spaces.

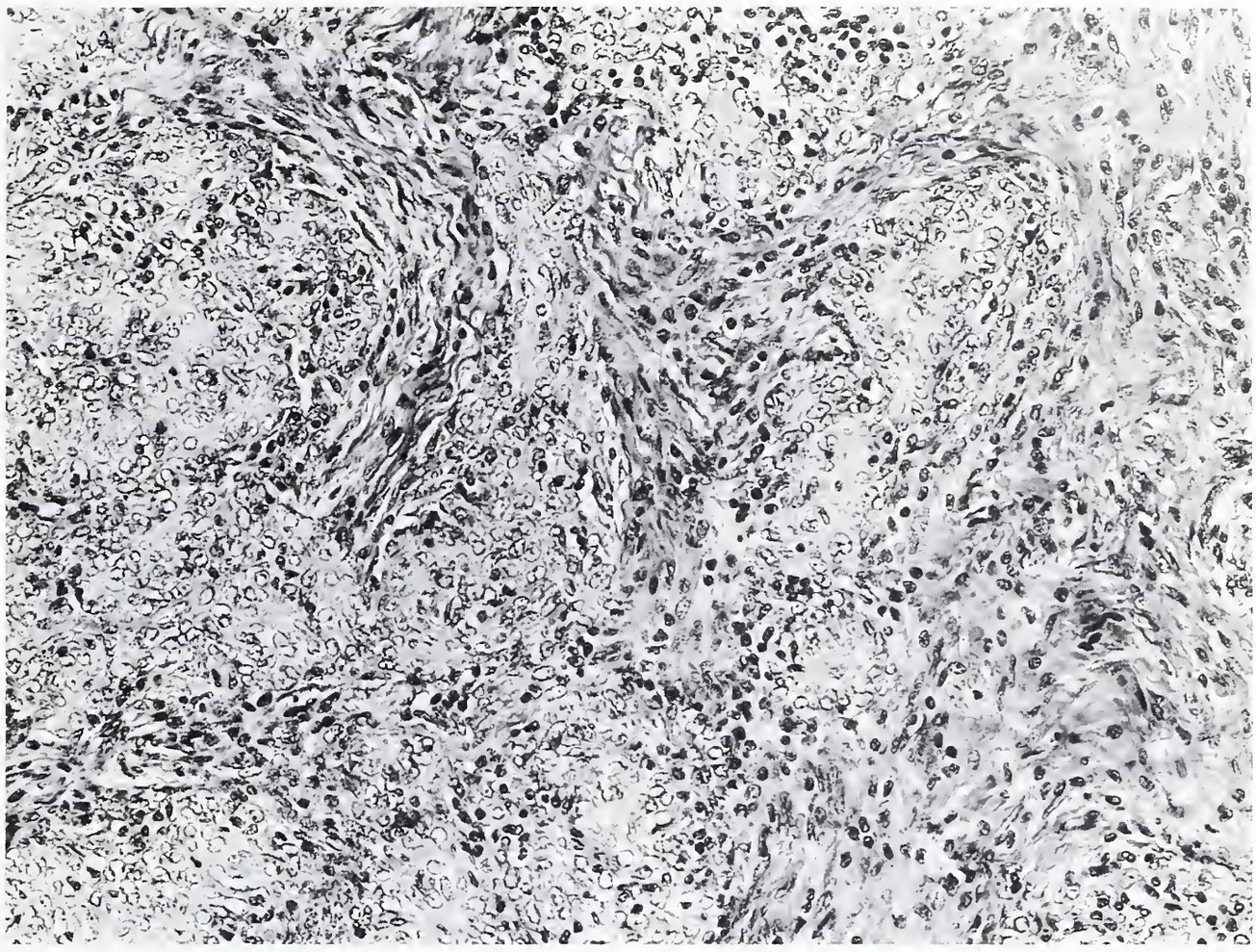


Figure 3-61
THYMOMA WITH ROSETTES AND SPINDLE TYPE EPITHELIAL CELLS
Aggregates of rosettes are subdivided by bundles of spindle-shaped epithelial cells.

3-57, 3-75, 3-77); and 3) tight intermingling of both components.

Predominantly cortical (organoid) thymoma is composed of lymphocyte-rich lobules bordered by thin, delicate fibrous tissue. The cortical type epithelial cells are fewer in number compared with those in the cortical type thymoma, and they possess smaller and less prominent nucleoli. Areas of medullary differentiation may be seen, which may contain Hassall corpuscles (figs. 3-55, 3-56). A starry sky appearance with macrophages may be found (fig. 3-54). Perivascular spaces are present and may be dilated (see fig. 3-38).

Cortical thymoma is composed of cortical epithelial cells, often arranged in sheets, with larger nuclei and more prominent nucleoli than those of predominantly cortical thymoma. There is a well-organized lobular architecture (see figs. 3-44–3-46) and foci of epidermoid differentiation. Perivascular spaces are narrow and foci of medullary differentiation are less distinct than in the predominantly cortical thymoma.

Well-differentiated thymic carcinoma (WDTC) is a predominantly epithelial tumor in which epithelial cells tend to be smaller than those in cortical thymoma and possess round to oval or irregular grooved nuclei, inconspicuous nucleoli, and clear or oxyphilic cytoplasm with well-defined cell borders showing epidermoid features (see figs. 3-47, 3-58). A slight to moderate degree of cellular atypia and mitoses of up to 10 per 10 high-power fields are noted. Palisading of epithelial cells toward the perivascular spaces and fibrous tissue is a characteristic feature (see figs. 3-42, 3-47). WDTC generally shows diffuse invasive growth, but a lobular growth pattern

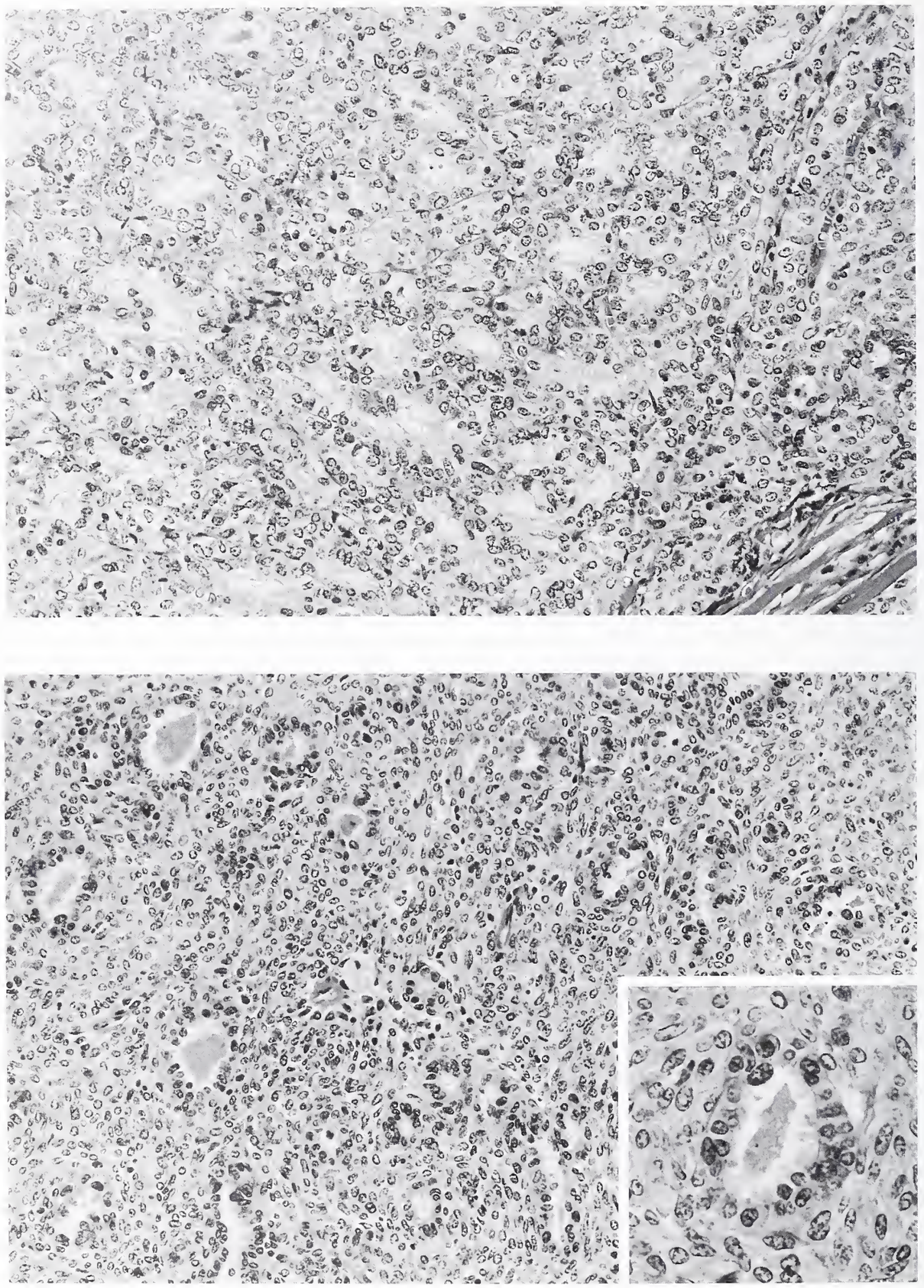


Figure 3-62
THYMOMA WITH GLANDS

Top: Cuboidal epithelial cells with basal nuclei and pale cytoplasm form small glandular spaces.

Bottom: In other areas, scattered glands show secretory activity with eosinophilic material in glandular lumina, which was PAS positive and alcian blue negative. Interposing short spindle cells were cytokeratin positive, although to a lesser extent than the glandular cells (see figure 3-78). Inset: High-power view of a gland.

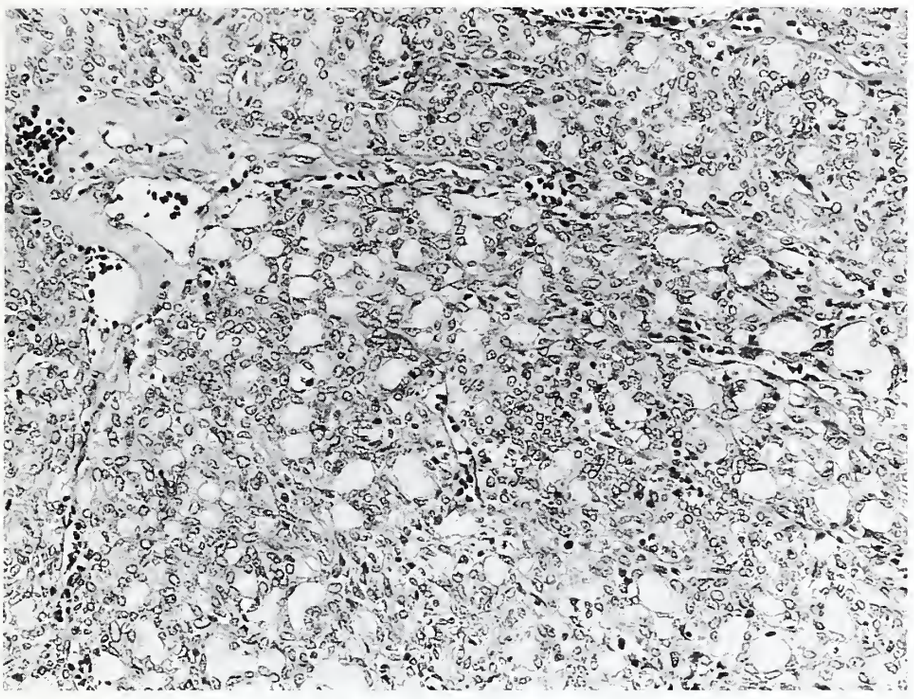


Figure 3-63
THYMOMA WITH
PSEUDOGLANDULAR SPACES

Many microcystic spaces lined by flat epithelial cells are present in an epithelial cell predominant thymoma. The microcystic lumen contains amorphous material. Individual tumor cells possess oval vesicular nuclei, inconspicuous nucleoli, and scanty cytoplasm.

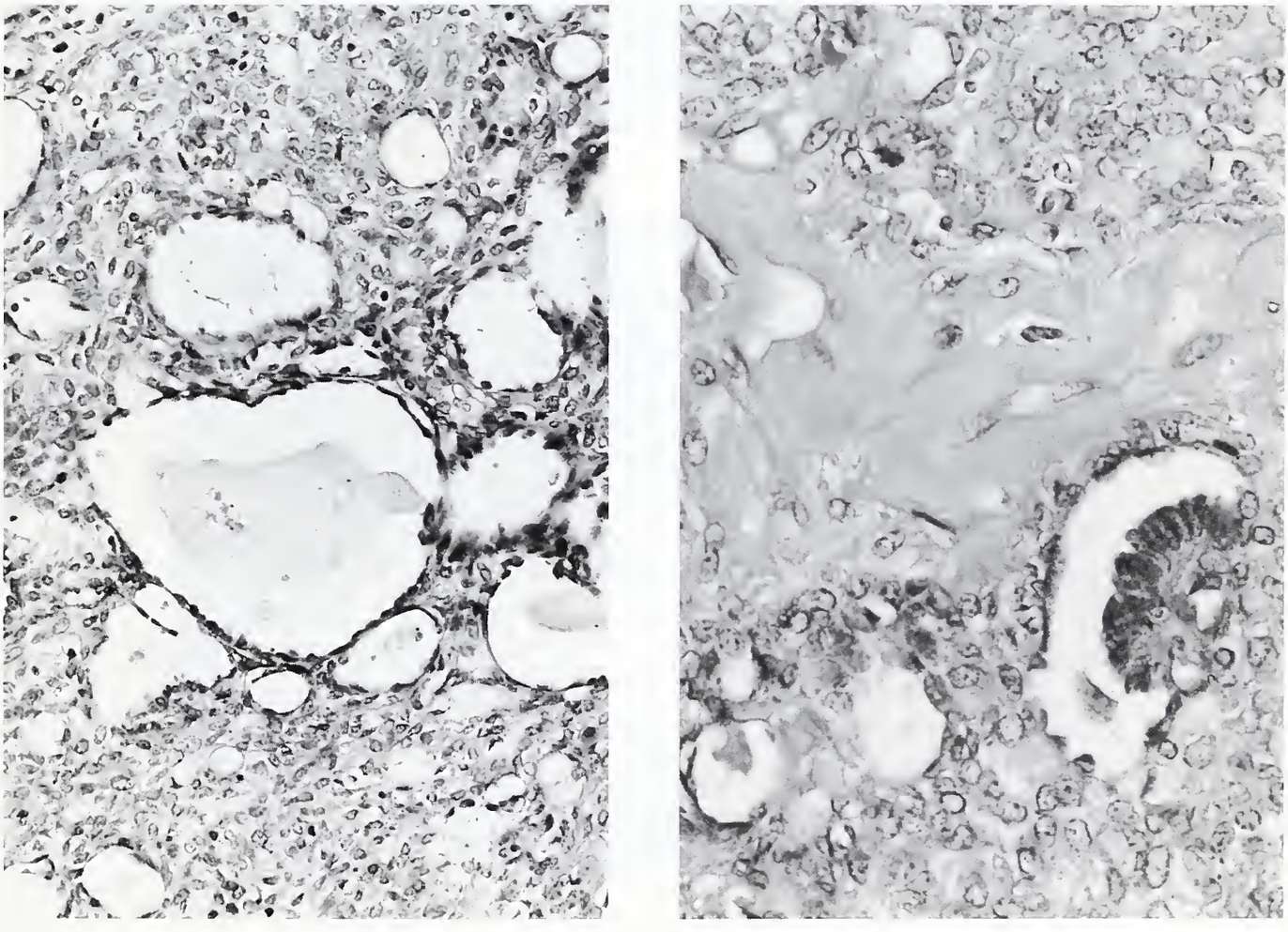


Figure 3-64
THYMOMA WITH PSEUDOGLANDULAR SPACES AND A GLOMERULOID STRUCTURE

Left: Scattered cystic spaces of various sizes are lined by flattened or cuboidal cells containing amorphous material.
Right: A single glomeruloid structure is present in a microcystic space (same case as that in figures 3-59, 3-63).

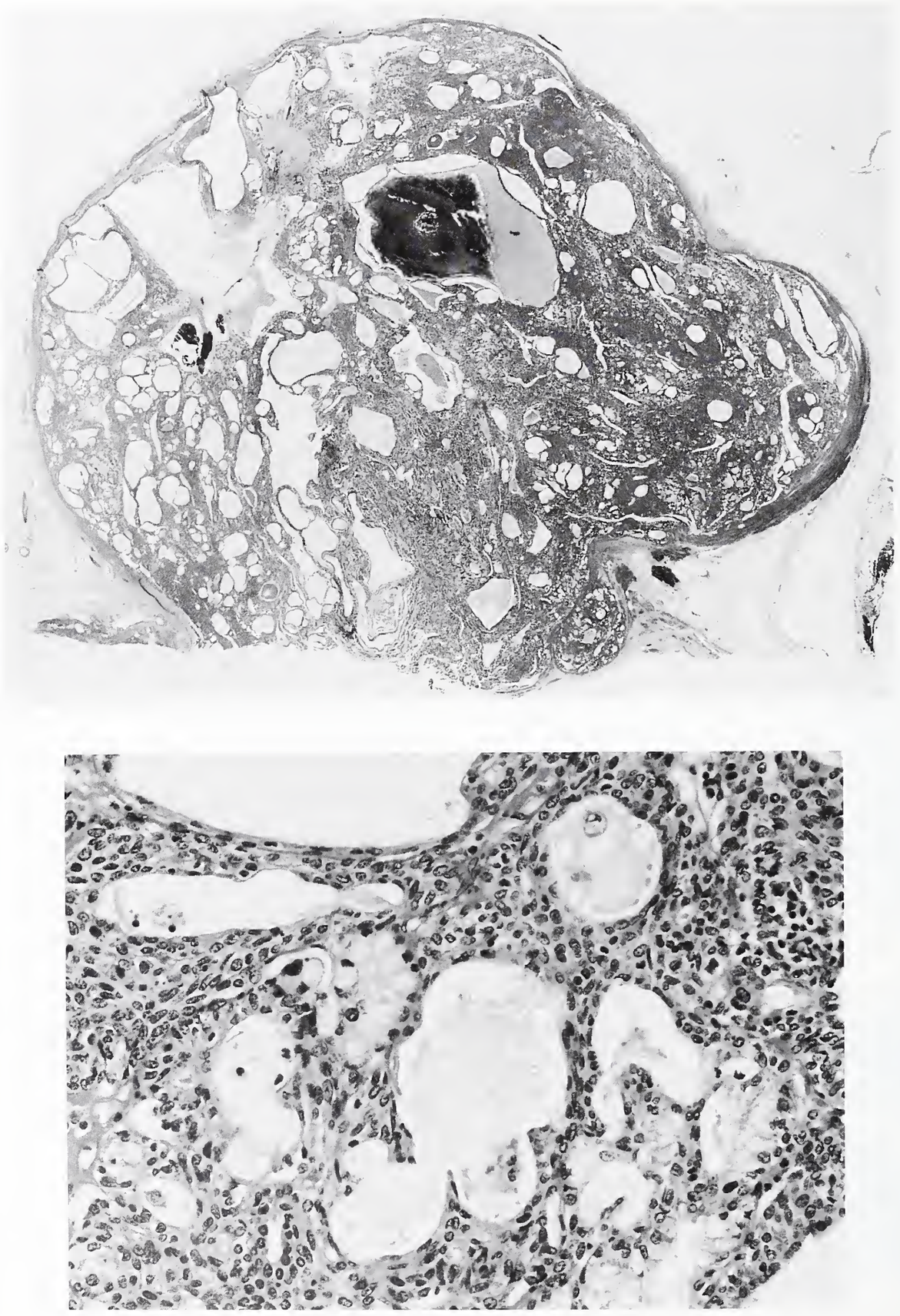


Figure 3-65
THYMOMA WITH MUCIN-PRODUCING GLANDS

Top: Low-power view shows encapsulation and multiple cysts.

Bottom: Besides cystic spaces of various sizes, there are several small glands lined by columnar cells with basal nuclei and foamy cytoplasm, which contained PAS- and alcian blue-positive epithelial mucin.

surrounded by sclerotic tissue may be seen. In WDTC, the architectural and cytologic features of thymoma can still be recognized and parts of the tumor contain areas with features of cortical thymoma. According to Kirchner et al. (53), the diagnosis is established when typical features of WDTC occupy over 50 percent of the entire tumor area, but according to Quintanilla-Martinez et al. (90) any significant component of the tumor with features of WDTC is sufficient for diagnosis.

Pescarmona et al. (88) reviewed 15 well-differentiated thymic carcinomas and justified their separation from thymoma because of histologic characteristics and aggressive biologic behavior. Later, they recognized histologic progression in five of nine recurrent thymomas with cortical differentiation from predominantly cortical thymoma to cortical thymoma and/or well-differentiated thymic carcinoma, usually associated with more advanced clinical stage (86a). Kuo et al. (61) compared the Müller-Hermelink system with the traditional classification in the evaluation of 71 thymomas, and supported the former system for predicting the aggressive potential of thymomas. Ho et al. (47) also supported the histogenetic classification for thymic epithelial tumors after evaluating 87 tumors from Chinese patients in Hong Kong. Quintanilla-Martinetz et al. (89), using the Marino-Müller-Hermelink-Kirchner system, concluded that histologic subclassification is an independent prognostic factor, predicting relapse and the risk of death from thymoma. Conversely, Pan et al. (84) concluded that "epithelial subtyping is not indispensable for diagnosis because long-term survival is not conspicuously influenced," although they recognized the merits of the Müller-Hermelink system.

Controversies surrounding histologic subtyping of thymoma include: 1) terminology used for the cell type (either based on cell morphology or based on histogenesis); and 2) separation of well-differentiated (organotypical, low grade) thymic carcinoma from cortical thymoma (100). If the traditional system using a subdivision into three types (predominantly lymphocytic, mixed lymphocytic and epithelial, and predominantly epithelial) is combined with epithelial cell morphology, that is, polygonal (round or oval) and spindle cell types graded by degree of atypia, and with tumor extension as circumscribed or invasive (see Table 3-2), a system of subtyping similar to that of Müller-Hermelink results. Since the cell of origin does not always determine the cell morphology, it is better not to use any term related to origin, but to stick to cell morphology for histologic classification. Well-differentiated thymic carcinoma can be classified as thymoma, predominantly epithelial polygonal cell type with atypia and increased proliferative activity, or simply as atypical thymoma. Table 3-5 presents the three representative classifications of thymic epithelial tumors currently used: those of Rosai and Levine (66,92), Müller-Hermelink and associates (53, 70), and this Fascicle, which is a modification of that of Wick et al. (110) and Lewis et al. (68).

Although it is said that the classifications proposed by Marino, Müller-Hermelink, and Kirchner et al. can be applied easily to most thymic epithelial tumors, the authors encountered some difficulty in deciding cell and histologic types because of the presence of histologically intermediate cell types. When the tumor cells are small and oval, it is difficult to know to which cell type they belong. Within each cell type there seems to be at least two distinct cell morphologies, although there are cells with features transitional between the two types. That is, cortical cells include cells with round vesicular nuclei, prominent nucleoli, and indistinct cell borders (see figs. 3-46, 3-53) and cells with granular, occasionally folded nuclei, inconspicuous nucleoli, moderate amount of cytoplasm, and distinct cell borders, which may have an epidermoid arrangement (figs. 3-47, 3-58, top). In the medullary type, tumor cells may be spindle shaped and fibroblastic, or oval and epithelial, with rosettes or glandular differentiation. The absence of Hassall corpuscles in medullary thymoma and their presence in cortical thymoma is also difficult to understand, as is the presence of "cortical cells" within foci of medullary differentiation. From these observations, it is apparent that further study on cell typing, cytogenesis, and appropriate terminology is required.

Less frequently observed cytologic and histologic variations in the epithelial cells of thymoma include marked squamous differentiation with formation of Hassall corpuscles, clear cell features, rosette-like formation, hemangiopericytoma-like areas, papillary foci, glandular or mucus formation, and scattered myoid cells.

Table 3-5

COMPARISON OF RECENT CLASSIFICATIONS OF THYMIC EPITHELIAL TUMORS

Degree of Malignancy	Levine and Rosai (1978 [37])	Müller-Hermelink et al. (1985 [40], 1992 [23])	Shimosato and Mukai (1997) (Modification of classification by Wick et al. [80] and Lewis et al. [38])	
Benign	Thymoma	Thymoma	Thymoma	
	Encapsulated (noninvasive)	Medullary type	Encapsulated	Spindle cell type
		Mixed type		Mixed spindle cell and polygonal cell type
			Nonencapsulated Circumscribed*	
Intermediate	Malignant Type I (invasive)	Predominantly cortical type		Polygonal cell type
		Cortical type	Invasive**	
(Borderline)		Well-differentiated carcinoma		With cellular atypia
Malignant	Malignant Type II (thymic carcinoma)	Thymic carcinoma	Thymic carcinoma	

*Confined to within the thymus or adherent to but not invading adjacent structures or organs.
**Invading adjacent structures or organs.

Squamous Cell Differentiation with Frequent Hassall Corpuscles. Metaplastic squamous cell nests may be seen at the site of a degenerative process, although rarely (fig. 3-66). Thymoma with marked squamous differentiation is rare, although a few Hassall corpuscles are seen in the mixed cell or lymphocyte-predominant thymoma (fig. 3-67). The Hassall corpuscles may be so mature that it is difficult to exclude the possibility of inclusion of non-neoplastic thymic tissue, particularly when the Hassall corpuscles are near the capsule facing non-neoplastic thymic tissue (fig. 3-56). Thymoma with marked squamous differentiation is entirely different from thymoma with scattered Hassall corpuscles, in which the bulk of the tumor is composed of epithelial cell nests with a tendency for keratinization, surrounded by intimately associated lymphocytes. Individual cells possess bland nuclei, seldom showing mitotic activity, and the cellular arrangement is entirely different from that of squamous cell carcinoma composed of solid tumor cell nests bordered by a stroma with lymphocytic infiltration (fig. 3-68).

Clear Cell Thymoma. Polygonal cells may possess abundant water-clear cytoplasm and centrally located, irregularly shaped or condensed small nuclei. A tumor composed predominantly of clear polygonal cells resembles renal cell carcinoma, but it can be distinguished from the latter by the presence of areas of polygonal cells with scanty cytoplasm, which are characteristic of epithelial cell–predominant thymoma, and the presence of perivascular spaces (fig. 3-69). However, such a case could well be interpreted as a developing clear cell carcinoma in an epithelial-predominant thymoma when nuclear atypia is considerable. On the other hand, the epithelial cells of thymoma at times show ballooning-type degenerative changes (fig. 3-70).

Rosette-Forming Cell Type. In the second series Fascicle rosettes were identified in 20 percent of thymomas (92) but in our experience they are less common, and thymomas with easily recognizable rosettes are rare. The rosettes are made up of epithelial cells with basal small nuclei, but do not form central lumina (95). The central portions of the rosettes are faintly eosinophilic and faintly fibrillar. A back-to-back arrangement of rosettes is the usual finding, with frequent lymphocytes rather than epithelial cells

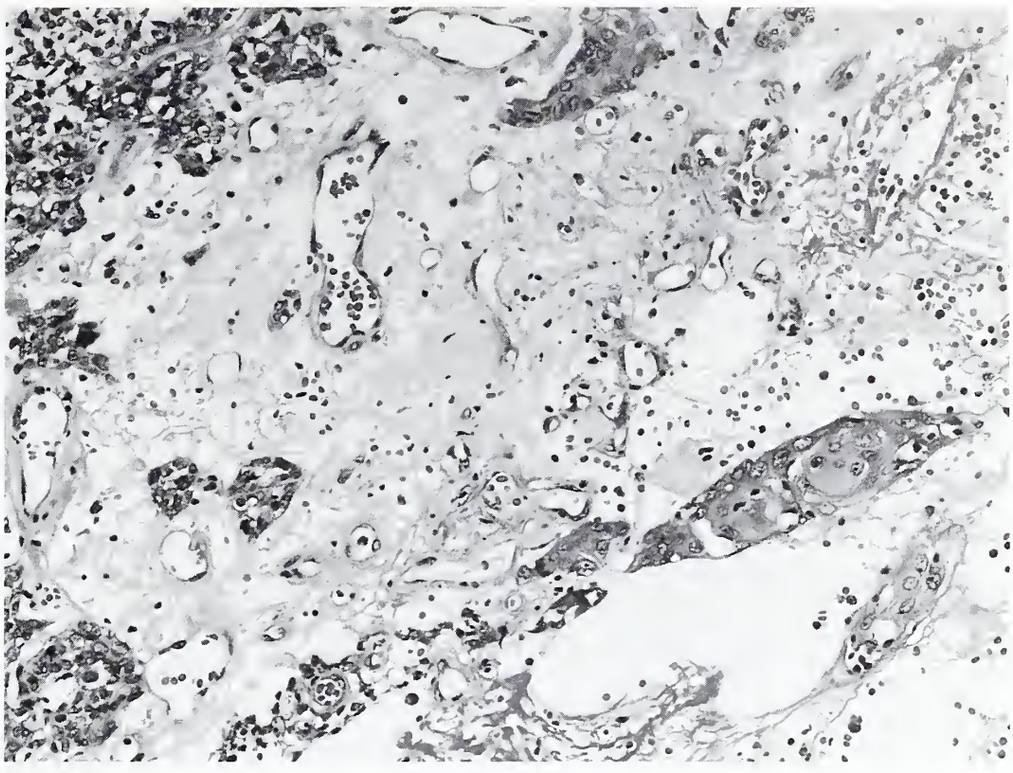


Figure 3-66
SQUAMOUS METAPLASIA IN THYMOMA

Within a degenerating focus of thymoma there are a few small nests of epithelial cells showing keratinization. They are considered to be secondary to degeneration rather than remaining Hassall corpuscles.

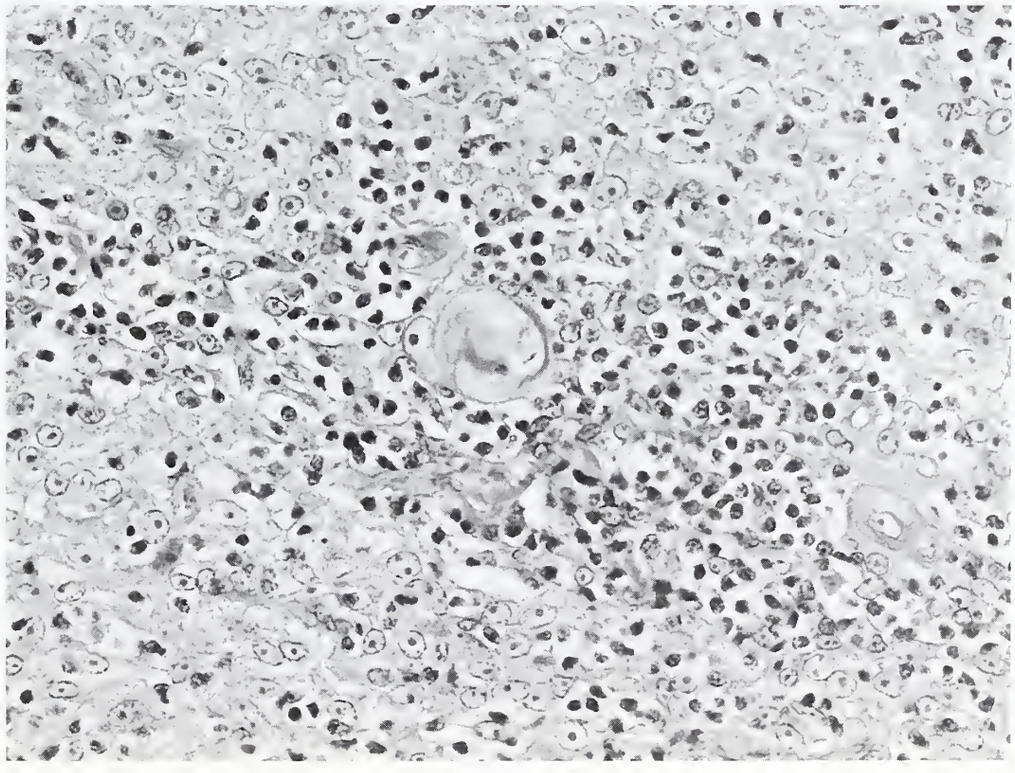


Figure 3-67
MIXED LYMPHOCYTIC AND EPITHELIAL THYMOMA CONTAINING HASSALL CORPUSCLES

A small keratinizing cell nest is present within the lymphocyte-rich zone. Note the resemblance of vesicular nuclei of some epithelial cells with prominent nucleoli in the nest to those in the surrounding area.

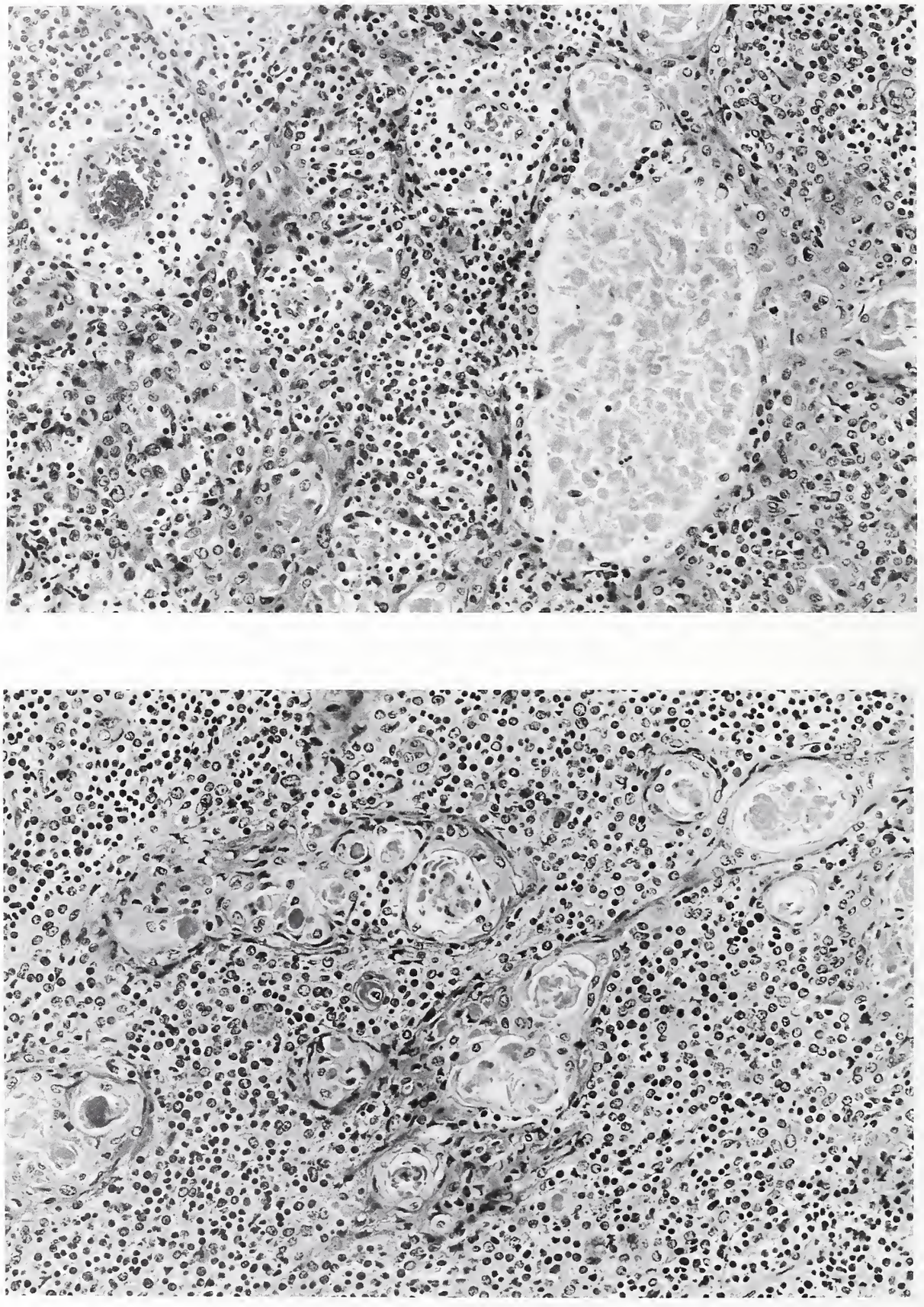


Figure 3-68
THYMOMA WITH MARKED SQUAMOUS CELL DIFFERENTIATION

Top: This mixed lymphocytic and epithelial thymoma displays marked squamous cell differentiation with abundant keratotic debris in some epithelial cell nests. Note a few perivascular spaces lined by flattened epithelial cells.

Bottom: Hassall corpuscle–like cell nests interconnect with each other. (Courtesy of Dr. Shojiro Morinaga, Tokyo.)

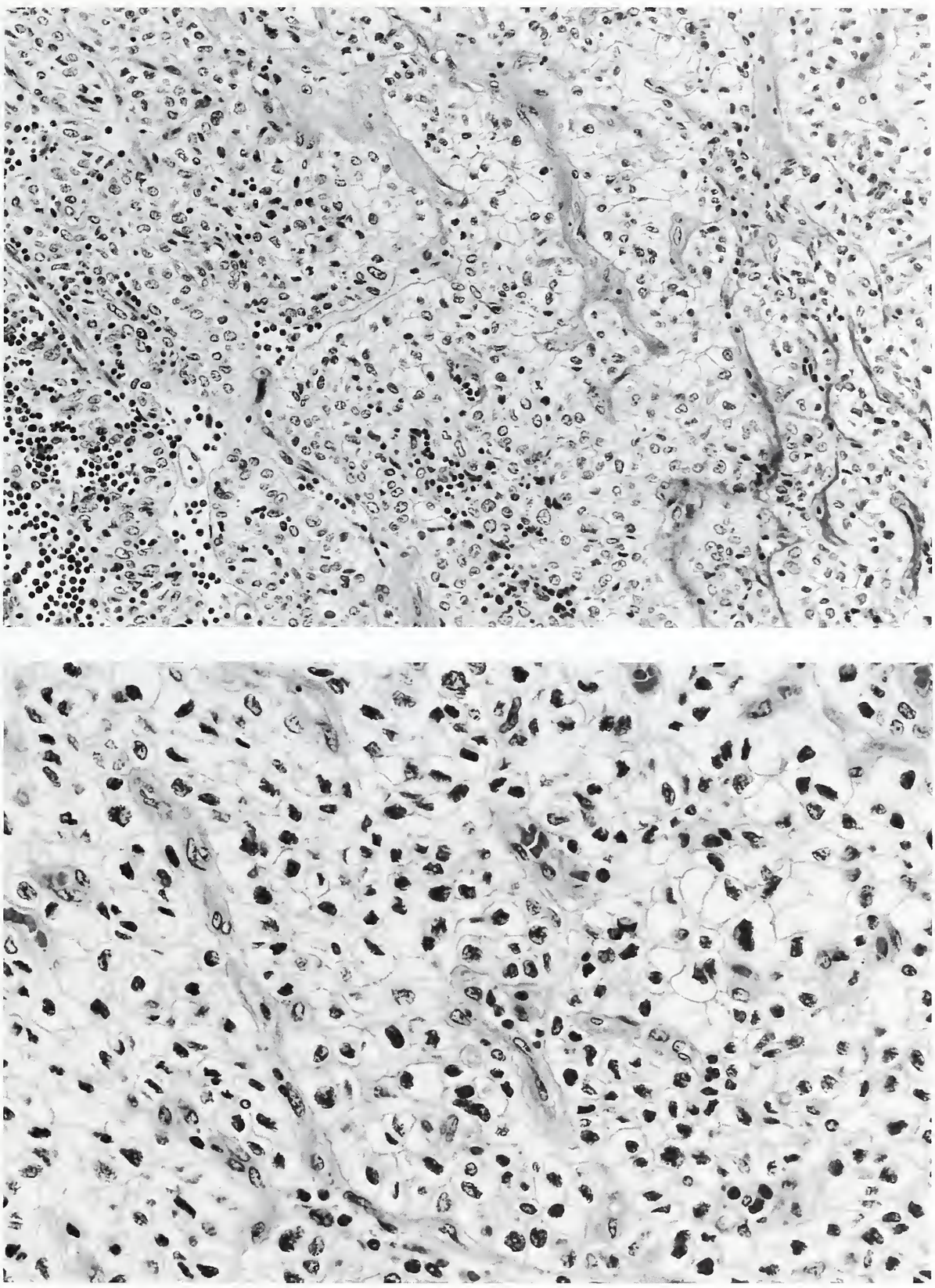


Figure 3-69
CLEAR CELL THYMOMA

Top: Diffuse growth of polygonal cells with slightly atypical nuclei and abundant water-clear cytoplasm resembles renal clear cell carcinoma, but features in the left lower corner are characteristic of thymoma, showing a mixture of lymphocytes and perivascular spaces.

Bottom: Higher magnification of clear cell areas with increased nuclear atypia and hyperchromasia, which are due either to degeneration or neoplastic progression. (Courtesy of Dr. Tadaaki Eimoto, Nagoya, Japan.)

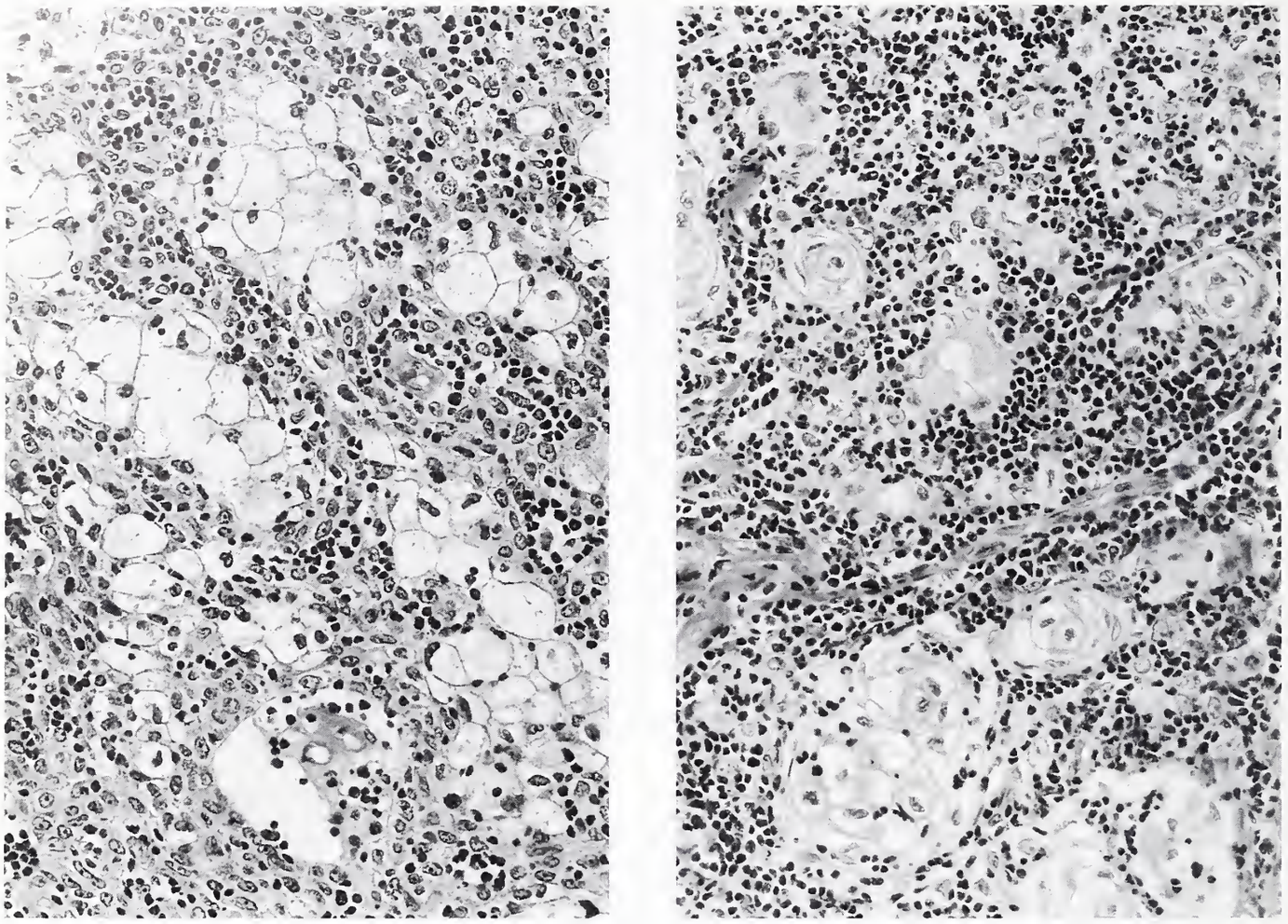


Figure 3-70
THYMOMA WITH BALLOONING DEGENERATION OF EPITHELIAL CELLS
Left: Within mixed lymphocytic and polygonal epithelial cell type thymoma, there are multiple small aggregates of ballooned epithelial cells with a tendency for cytolysis.
Right: Ballooning may also be seen in epithelial cells showing squamous differentiation. (Right and left are from different cases.)

interposed between them (fig. 3-60). However, there are cases showing bundles of spindle-shaped epithelial cells associated with rosettes (fig. 3-61). Many of the spaces between the rosettes are artifactual, produced by tissue processing. Rosette-forming cells are cytokeratin positive, without neuroendocrine markers or argyrophilia. Rosette-forming cells are considered to be medullary type epithelial cells, as are the cells arranged in pericytomatous and glandular patterns.

Thymoma with Hemangiopericytoma-like Features. Small nests and trabeculae of short, spindle, oval to round epithelial cells may be closely associated with a fine vasculature, reminiscent of hemangiopericytoma (fig. 3-59). However, there are other features characteristic of thymoma, and no smooth muscle actin can be demonstrated in pericytoma-like areas. True primary hemangiopericytomas in the thymus or mediastinum are extremely rare, and only a single documentation was cited by Enzinger and Weiss (41). Therefore, tumors of the mediastinum with hemangiopericytoma-like areas should be examined carefully for features typical of thymoma.

Thymoma with a Papillary Pattern, Glands, and Gland-like Spaces. Microcystic, dilated, or collapsed tubular spaces lined by cuboidal or flattened cells may be found in thymoma; the spaces are either empty, or contain amorphous eosinophilic material or cellular debris (figs. 3-63; 3-64, left; 3-65, top). When these structures are seen in and near the capsule, the possibility of inclusion of mesothelial cells or preexistence of minute thymic cysts should be considered. A

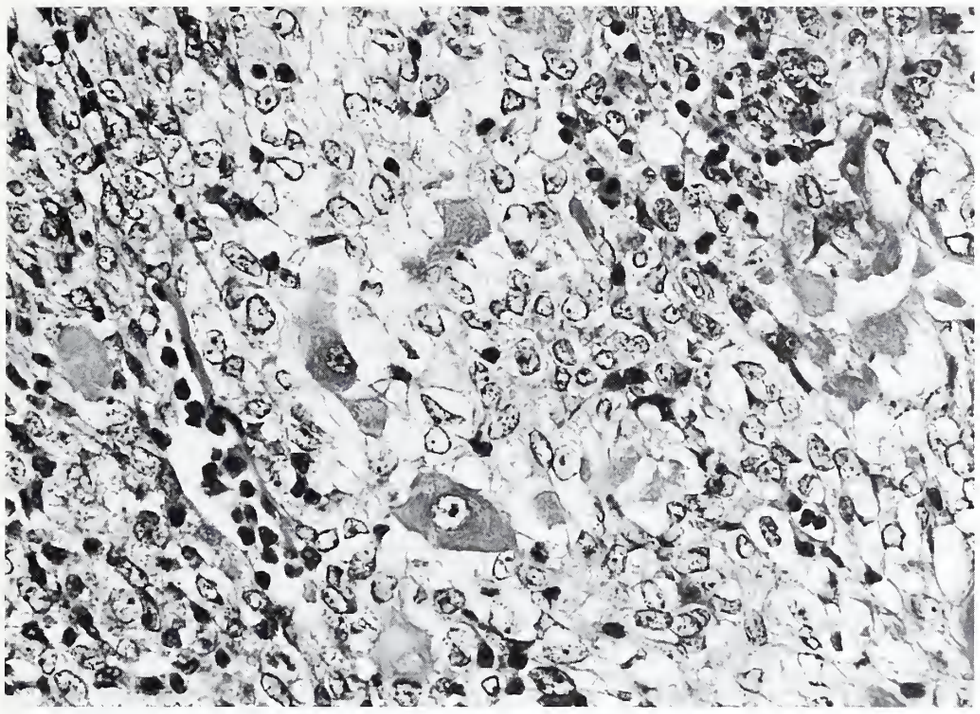


Figure 3-71
THYMOMA WITH MYOID CELLS
Scattered within the tumor tissue are irregularly shaped large cells with vesicular nuclei, prominent nucleoli, and abundant deeply eosinophilic fibrillar cytoplasm. The cytoplasm of these cells was strongly positive for myoglobin.

papillary arrangement of cuboidal epithelial cells may also be seen, although infrequently. A glomeruloid body was noted in a single instance in our series (fig. 3-64, right).

Microscopic foci of cystic spaces due to liquefactive degeneration of thymoma are common, and may be empty or contain cellular debris. Some cystic spaces become large enough to be seen with the naked eye, and are sometimes filled with proteinaceous material or foamy histiocytes. In rare cases, most or all of the lesion becomes cystic (104).

True glandular spaces may also be found in thymoma. These are often small and lined by cuboidal or low-columnar cells, with or without cytoplasmic projections. They contain no visible material or PAS-positive eosinophilic secretion, and are surrounded by diffuse growth of oval to short spindle-shaped epithelial cells (fig. 3-62). Rarely, the cytoplasm and glandular lumen contain epithelial mucin (fig. 3-65).

Thymoma with Myoid Cells. Large, polygonal or round myoid cells with abundant eosinophilic fibrillar cytoplasm may be scattered in the tumor; these cells are positive immunohistochemically for desmin, actin, and myoglobin (fig. 3-71). Cross striations may be evident in these cells upon light and electron microscopic examination (fig. 3-72). The presence of myoid cells in normal thymic tissue, particularly in the medulla, supports the appearance of such cells in neoplastic conditions (45,46), and these are considered to be transformed epithelial cells. Recently, Moran et al. (74) reported a rare case of thymoma containing numerous myoid cells, which they designated *rhabdomyomatous thymoma* (fig. 3-73). The presence of myoid cells is not associated with complicating myasthenia gravis.

Extremely Rare Forms of Thymoma. We have noticed scattered, melanin-containing, spindle to polygonal cells located singly or forming small aggregates among spindle-shaped epithelial cells in a predominantly epithelial thymoma. These are melanocytes, which may have originated from neuroectodermal cells present in the thymic tissue (fig. 3-74). However, neural features could not be demonstrated in the tumor immunohistochemically, except for S-100 positivity in both polygonal and spindle epithelial cells (see fig. 3-77). The presence of non-neoplastic melanocytes was also described in a thymic carcinoid tumor (48).

Some thymomas may be composed of aggregates of polygonal epithelial cells and intervening bundles of spindle-shaped epithelial cells (fig. 3-75). At a glance, these look like sarcomatoid carcinoma or malignant biphasic mesothelioma, but the nuclei are bland with little mitotic activity. Keratin immunostaining reveals a markedly positive reaction in the polygonal cells and occasional positivity in the spindle cells.

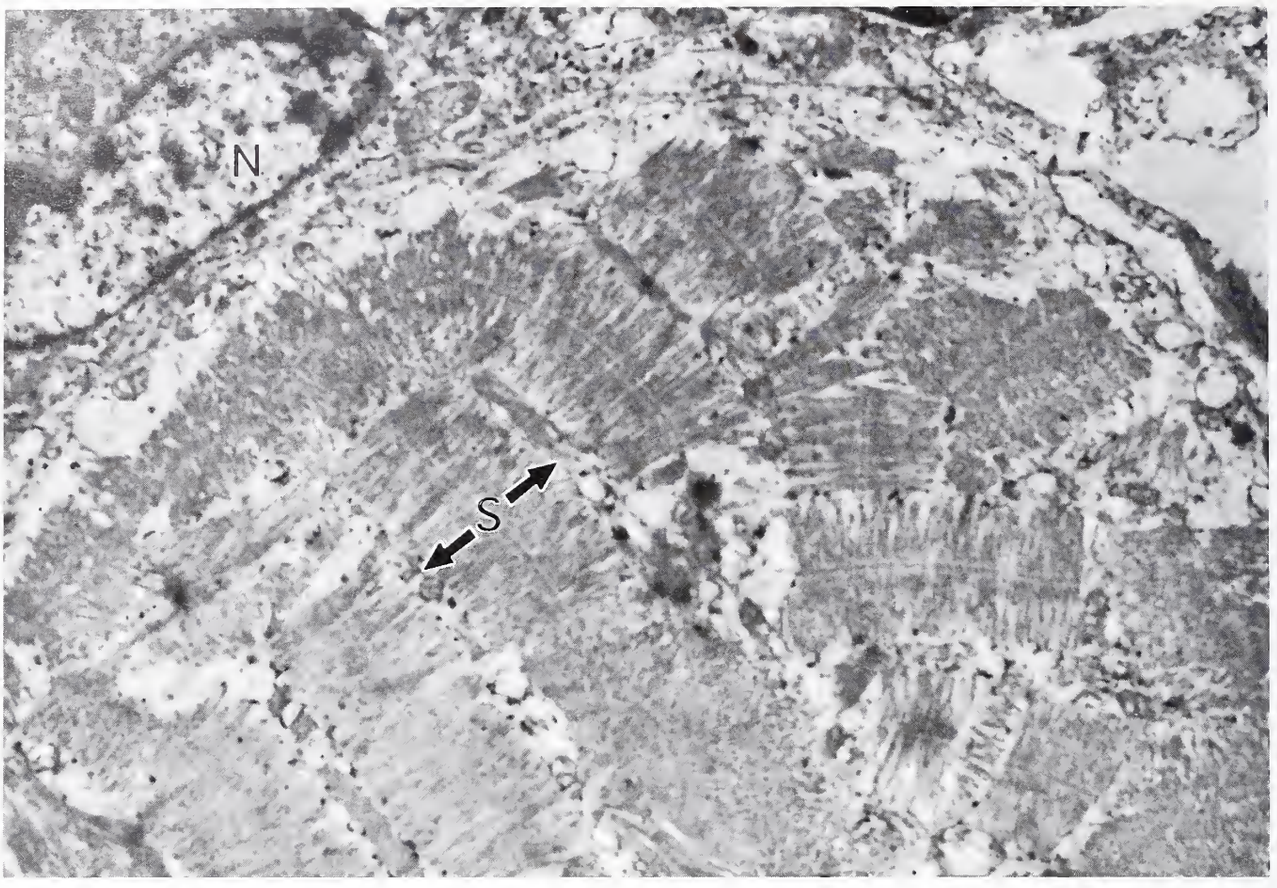


Figure 3-72
THYMOMA WITH MYOID CELLS

Electron micrograph shows that the cells contain numerous sarcomeres (S). The nucleus (N) belongs to a neighboring epithelial cell (X13,300). (Fig. 85 from Fascicle 13, 2nd Series.)

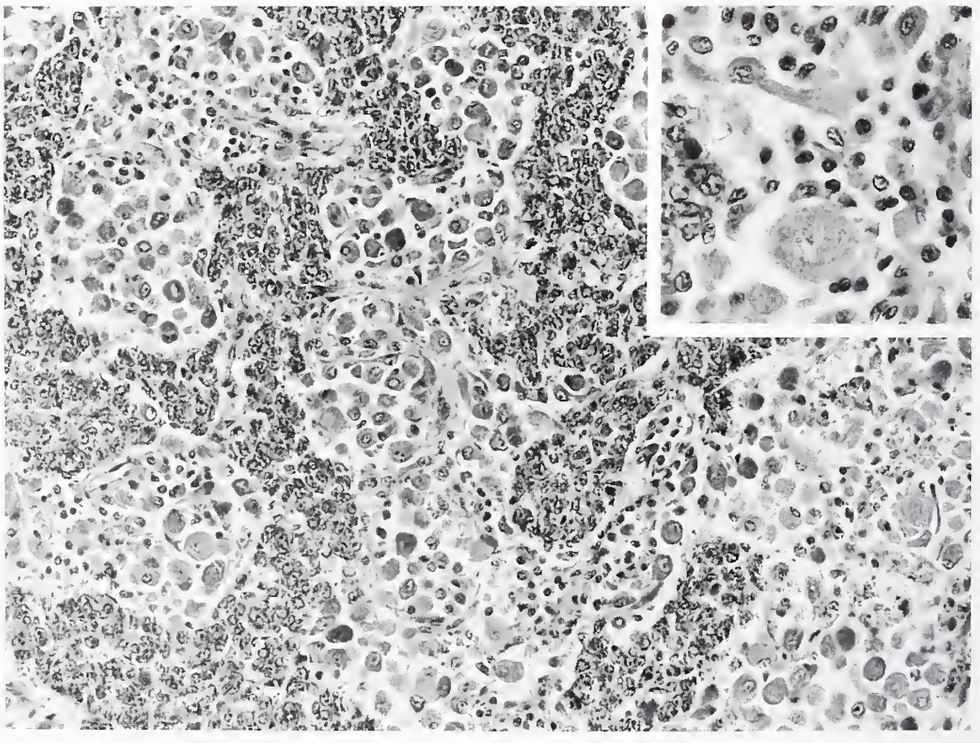


Figure 3-73
RHABDOMYOMATOUS THYMOMA

Between irregularly shaped nests of polygonal epithelial cells with vesicular nuclei and scanty cytoplasm are numerous loosely arranged rhabdoid cells and some lymphoid cells. Inset shows a higher magnification view of the tumor containing tadpole-shaped and round rhabdoid cells with a fibrillar cytoplasm. (Courtesy of Dr. Cesar A. Moran, Washington, D.C.)

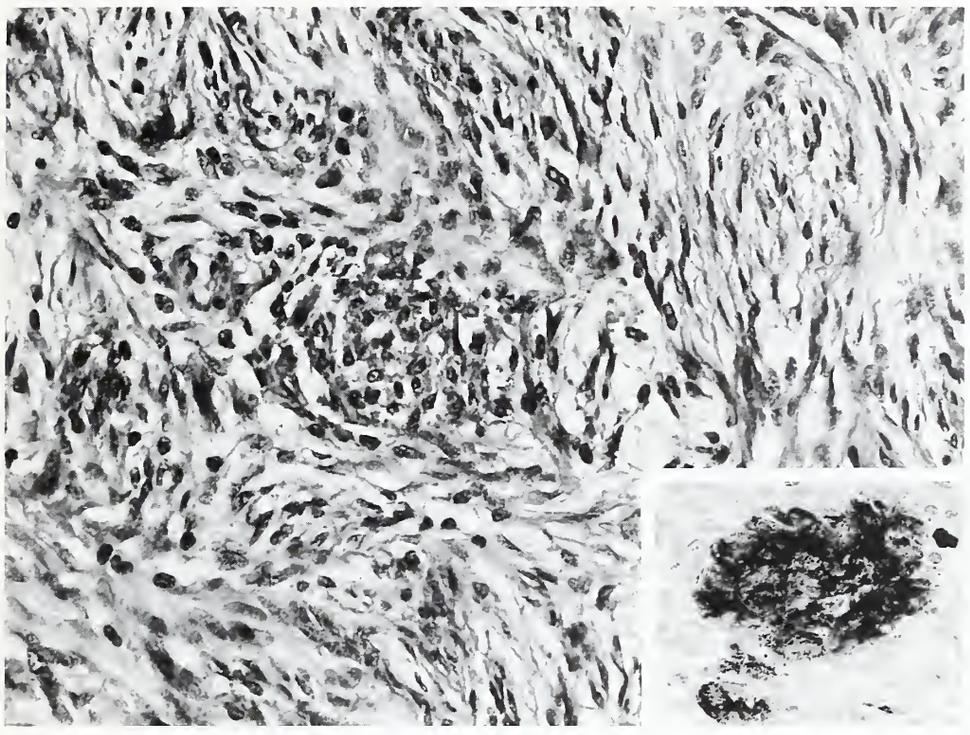


Figure 3-74
THYMOMA WITH MELANOCYTES
Within the growth of spindle cells there is a polygonal cell nest with cytoplasmic brown (melanin) pigments. Inset: Melanin-containing cells are present singly and in an aggregate (without eosin counterstain).

Two cases of sclerosing thymoma, one each of predominantly epithelial and predominantly lymphocytic types, were reported by Kuo (59), who considered sclerosis to be a phenomenon of spontaneous regression. A case of plasma cell–rich thymoma was reported by Moran et al. (76) in which a polyclonal hypergammaglobulinemia of unknown cause subsequently developed.

Differential Diagnosis. Differentiating thymoma from other thymic tumors is based not only on histology but on other diagnostic approaches as well, such as immunohistochemistry, electron microscopy, and, in the future, genetic methods. However, in this section emphasis is placed on tumor histology and cytology.

In this Fascicle, type I malignant thymoma of Levine and Rosai (66) and most of the well-differentiated carcinomas described by Müller-Hermelink and associates (53) correspond to invasive thymoma, with or without metastasis. However, a few cases of well-differentiated carcinoma as defined by Müller-Hermelink do present diagnostic difficulties. Such tumors are characterized by a predominance of epithelial cells with a scant or absent lymphoid component. These epithelial cells have a polygonal shape, vesicular nuclei, prominent nucleoli, and occasional mitotic figures (see fig. 3-51). The arrangement of the epithelial cells may suggest "epidermoid" metaplasia (see fig. 3-58). However, the general features of thymoma, such as partial encapsulation, lobulation, and perivascular spaces, as well as cytologic features including a wrinkled or folded nuclear membrane, are of help in diagnosing thymoma. If features of typical thymoma are found, such as areas of mixed lymphocytic and epithelial thymoma, a diagnosis of predominantly epithelial thymoma with cellular atypia and increased proliferative activity can be established. However, for these tumors, some may prefer a diagnosis of thymic carcinoma originating in thymoma. In our experience, these tumors are obviously invasive, but rarely metastasize via blood vessels, and their biologic behavior is not very different from that of conventional invasive thymoma. Thus they may be categorized as "borderline" lesions at present.

An important consideration in routine practice is distinguishing invasive thymoma (type I malignant thymoma) from thymic carcinoma (type II malignant thymoma) which also includes carcinoma developing in thymoma. Carcinoma very often shows invasive growth at the advancing borders of the tumor, whereas invasive thymoma frequently shows encapsulation in some parts, and at times even in the advancing border, such as in the lung. Also, sclerosis, particularly in the center of the tumor, is seen more frequently

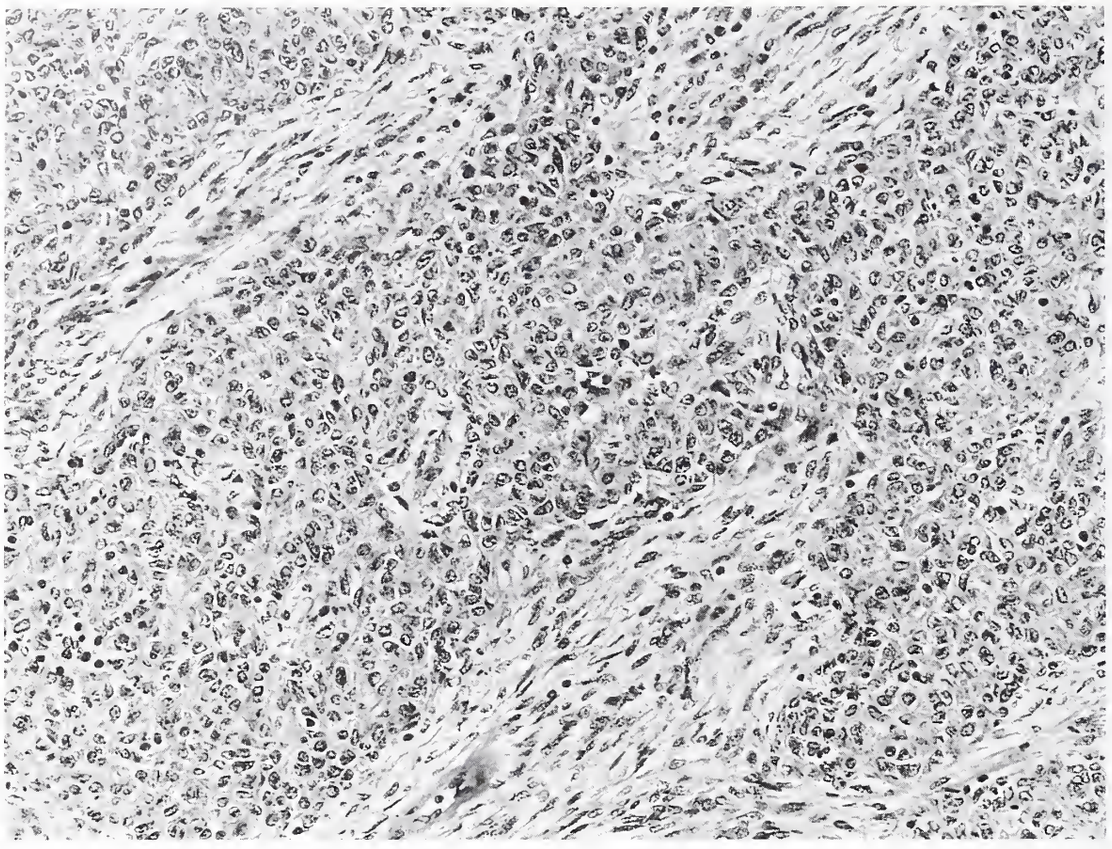


Figure 3-75
EPITHELIAL CELL PREDOMINANT BIPHASIC THYMOMA
The tumor is composed of irregularly shaped solid nests of polygonal cells and bundles of spindle cells, somewhat resembling malignant mesothelioma of the biphasic epithelial and fibrous type.

in thymic carcinoma. Although liquefactive necrosis forming various-sized cystic spaces is not uncommon in thymoma, coagulation necrosis is less frequent as compared with thymic carcinoma. The cells of thymic carcinoma are very atypical and can be easily distinguished from those of invasive thymoma, which frequently possess bland nuclei (101,107). As stated above, however, some thymomas may have atypical nuclei with some growth activity, like those in the well-differentiated carcinoma defined by Kirchner et al. (53). The number of mitotic figures is not a useful distinguishing feature, unless it is very high. However, atypical mitotic figures are almost nonexistent in thymoma, and their presence strongly suggests carcinoma. Inflammatory cells are seen most frequently in the stroma of carcinoma rather than the parenchyma. Plasma cells and eosinophils are seen occasionally in carcinoma, but rarely in thymoma.

It is on the basis of these general features that thymoma with frequent Hassall corpuscles can be distinguished from keratinizing squamous cell carcinoma. Perivascular spaces, which were once considered to be peculiar to thymoma, may be seen in some carcinomas (e.g., basaloid carcinoma). In addition, basaloid carcinoma is frequently encapsulated, and encapsulation together with perivascular spaces suggest borderline malignancy. However, cytologic atypia defines it as carcinoma, and in fact, it has been categorized into the low-grade malignancy group by Suster et al. (105).

Clear cell carcinoma, which possesses small nuclei like those seen in renal cell carcinoma, should be differentiated from epithelial cell predominant thymoma with clear cells. In the latter, the tumor is at least partly encapsulated and shows typical features of thymoma in some parts, such as oval cells with a distinct cell membrane and perivascular spaces (see fig. 3-69). Mucoepidermoid carcinoma, which is classified as low-grade carcinoma by Suster and Rosai (105), possesses normochromic, round and uniform nuclei

with little pleomorphism. When encapsulated and containing perivascular spaces, its histologic classification is problematic. As with mucoepidermoid tumors of accessory gland origin having myoepithelial cells in other organs, some mucoepidermoid tumors may, in fact, behave as benign thymic tumors. This entity could well be thymoma with bidirectional differentiation.

Besides morphology, the presence of paraneoplastic syndromes, particularly myasthenia gravis, is important for distinction between the two categories. In our experience, myasthenia gravis has never been noted in patients with thymic carcinoma, except when it coincidentally developed from typical thymoma. The high incidence of myasthenia gravis in "well-differentiated carcinoma" defined by Kirchner et al. (53) is an additional reason why we prefer to classify that tumor as an invasive thymoma.

Other tumors to be differentiated from thymoma include Hodgkin's disease, diffuse lymphoblastic lymphoma of the T-cell type, diffuse small cell lymphoma, and atypical carcinoid tumors. Germ cell tumors and diffuse large cell lymphoma with sclerosis can be differentiated from thymoma with relative ease, but possibly with some difficulty from thymic carcinoma.

Although the nodular sclerosis type Hodgkin's disease was interpreted as granulomatous thymoma in the past (62), the presence of lacunar cells and a variety of inflammatory cells and the absence of epithelial cells distinguishes these two tumors. Non-Hodgkin's lymphoma can also be diagnosed correctly by the absence of epithelial cells and the presence of mitotic figures in the lymphoid cells, mitoses being particularly frequent in the lymphoblastic type.

Differentiation between spindle cell thymoma and benign localized fibrous tumor of the pleura can be determined histologically in most cases; if difficulty persists, immunohistochemistry for cytokeratin and CD34 should be performed (see figs. 3-218, 3-219).

Immunohistochemistry and Functional Correlation. The utilization of immunohistochemistry for the differential diagnosis of thymic tumors and tumors of other organs has been described in the previous sections. Here we summarize the immunohistochemical features of thymoma in comparison with those of various thymic tumors. An immunohistochemical approach is necessary for the characterization of both epithelial cells and lymphocytes. For the preservation of antigens and morphology, cold acetone fixation of tissues followed by paraffin embedding is recommended in addition to routine formalin fixation (97).

Epithelial cells of the normal thymus derived from the third pharyngeal pouch can be divided into subcapsular, cortical, and medullary epithelial cells. Müller-Hermelink and associates (80, 81) reported that thymomas can be differentiated into those showing cortical or medullary phenotypic differentiation by using monoclonal antibodies such as 35 beta-H11 (against non-squamous type keratin) and 34 beta-E12, IV/82 (against squamous type keratin), respectively. According to them, the prognosis of patients with thymoma with a medullary epithelial cell phenotype was much better than for those with thymoma with a cortical epithelial cell phenotype. However, the former phenotype corresponds to spindle cell type thymoma, which is already known to show a more favorable outcome (68). Although van der Kwast et al. (108) divided thymomas into those composed mainly of cortical epithelial cells and those of medullary epithelial cells using monoclonal antibodies anti-HLA-DR and ER-TR5, and Chilosi et al. (39) found that variable numbers of spindle cells in most mixed thymomas, i.e., medullary type epithelial cells, were positive for B-cell marker CD20/L26, there are no known antibodies available at present that are specific for either cortical or medullary epithelium cells. Therefore, we subdivide thymoma by cell shape. In practice, the most important thymic epithelial cell antigen is cytokeratin. As already mentioned, recognition of a few epithelial cells in a lymphocyte-predominant thymoma can easily be done by immunostaining for cytokeratin, using antibodies recognizing both high and low molecular weight cytokeratins (fig. 3-76). The presence of cytokeratin-positive cells in a spindle cell tumor indicates the epithelial cell nature of the tumor (figs. 3-50, 3-77, 3-78). At present, the authors are not aware of any antibodies that can distinguish non-neoplastic thymic epithelial cells occasionally present within thymoma as inclusions and neoplastic cells.

Cytokeratin immunoreactivity is also useful for differentiating thymic epithelial tumors from other thymic neoplasms. Examples of tumors

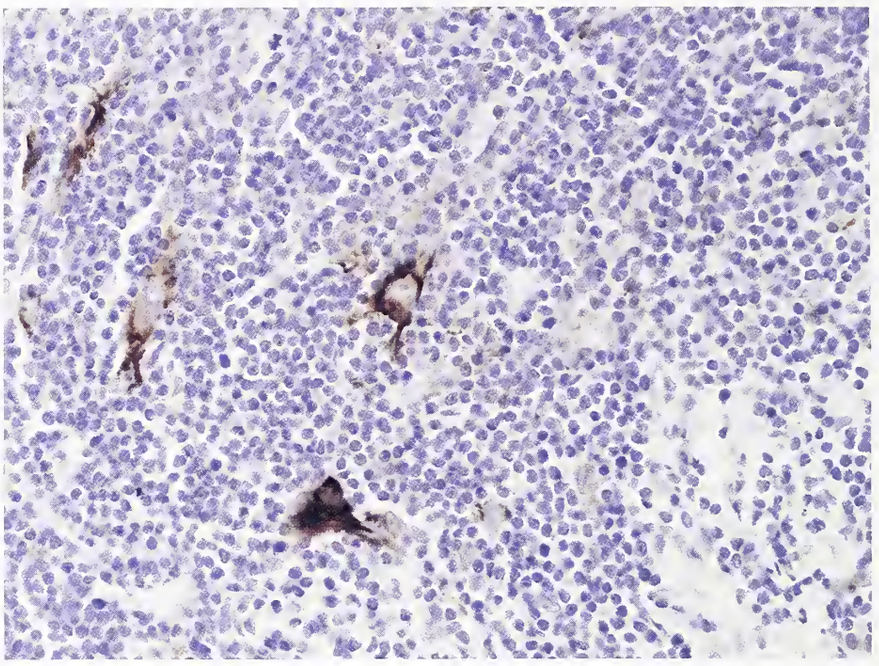
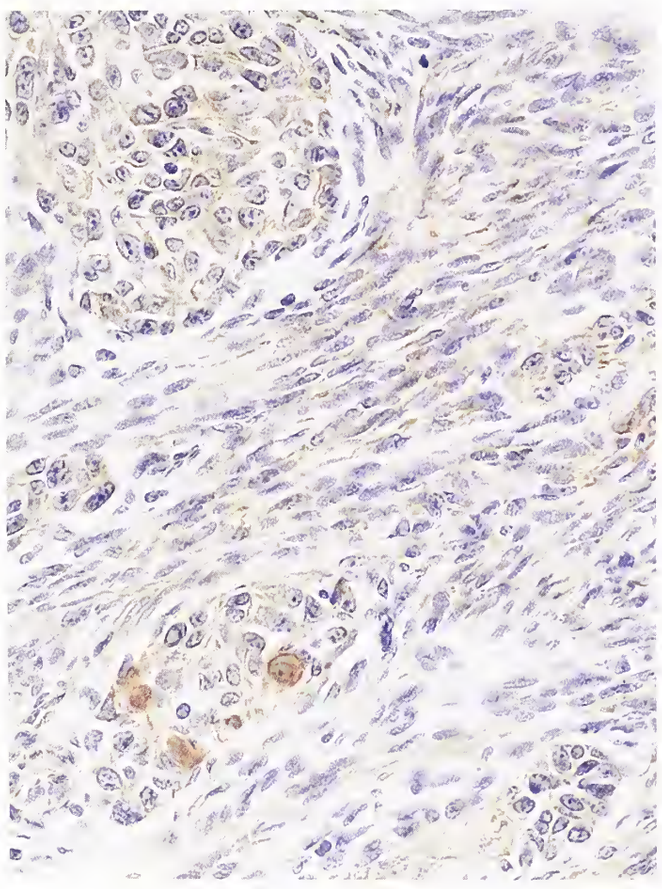


Figure 3-76
THYMOMA, LYMPHOCYTE-PREDOMINANT TYPE

Scattered among the densely packed lymphocytes are cells with vesicular nuclei, prominent nucleoli, and cytoplasmic processes, which stain strongly for cytokeratin (same case as that in figure 3-11). (Immunostaining for cytokeratin)



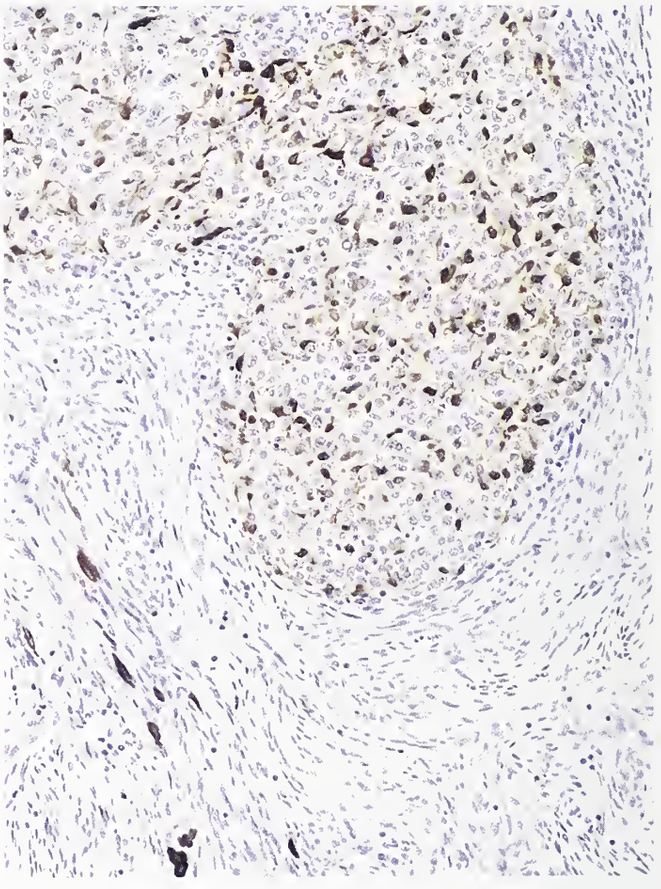


Figure 3-77
THYMOMA, PREDOMINANTLY EPITHELIAL, MIXED POLYGONAL AND SPINDLE CELL TYPE

Left: Both polygonal and spindle cells contain immunoreactive cytokeratin; the reaction is somewhat stronger in the former. (Immunostaining for cytokeratin)

Right: Many S-100 protein-positive cells are present in a polygonal epithelial cell nest, but pigmented cells appear negative (same case as that in figure 3-74). (Immunostaining for S-100 protein)

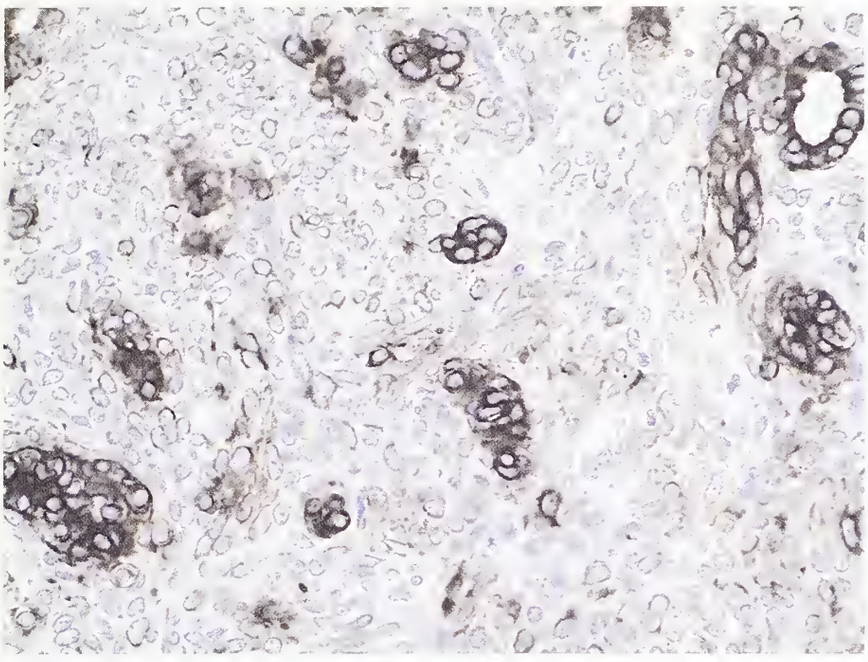


Figure 3-78
THYMOMA WITH GLANDS
Cuboidal and oval cells forming tubules and small nests are strongly reactive for cytokeratin, and oval to short spindle cells between the cell nests are less intensely stained (same case as that in figure 3-62). (Immunostaining for cytokeratin)

negative for cytokeratins include nodular sclerosis type Hodgkin's disease and diffuse large cell lymphoma with sclerosis (B-cell type), which may resemble undifferentiated carcinoma or atypical germinoma (seminoma).

CD57 (Leu-7), which is present in the subcapsular cortical epithelial cells of the thymus, is often immunohistochemically positive in the epithelial cells of thymoma (figs. 3-79, 3-80) (55). It has not been detected thus far in thymic squamous cell carcinoma. Therefore, it may be used to differentiate thymoma from thymic squamous cell carcinoma. However, in the lung, CD57 has been shown to be positive in small cell carcinoma and differentiated adenocarcinoma, and so there is a possibility that some thymic carcinomas may show such immunoreactivity.

With regard to myasthenia gravis, Kirchner et al. (52,54) reported that neoplastic epithelial cells in 15 of 17 thymic epithelial tumors associated with myasthenia gravis, but only 2 out of 8 tumors not so associated showed cytoplasmic acetylcholine receptor-related antigenic determinants, but no epitopes of the extracellular main immunogenic region.

Changes in expression of HLA antigens have been shown to occur at the time of neoplastic changes. Matsuno et al. (unpublished data, April, 1990) investigated the expression patterns of beta-2-microglobulin, the light chain of HLA class 1 antigen, and the alpha chain of HLA-DR class 2 antigen on 17 thymomas and 16 thymic carcinomas. Only 2 cases of thymoma with metastasis showed diffuse immunostaining for beta-2-microglobulin on the cytoplasmic membrane, whereas the remaining 15 cases without metastasis were negative or showed only focal immunostaining (figs. 3-81, 3-82). In contrast, 7 cases of thymic carcinoma showed diffuse staining and only 3 were negative. A similar result was obtained for the alpha chain of HLA-DR class 2 antigens: none of the thymomas showed diffuse staining, whereas 8 thymic carcinomas stained diffusely and the remaining 8 stained focally; there were no unreactive cases. These results indicate that expression of beta-2-microglobulin and the alpha chain of HLA-DR is seen in thymoma with metastasis and in many cases of thymic carcinoma.

Thymic lymphocytes (thymocytes) can be divided into medium-sized cortical (or immature) lymphocytes and small medullary (or mature) lymphocytes. The former possess granular, round or convoluted nuclei; visible nucleoli; and narrow basophilic cytoplasm with scanty organelles and are characterized by a CD1a+, CD3+, and CD4+ and CD8+ phenotype (double-positive thymocytes). Mitotic figures are observed. The latter possess wider clear cytoplasm and small condensed nuclei, and are characterized by a CD1a-, CD3+, and CD4+ or CD8+ phenotype (single-positive thymocytes). Both types of lymphocytes can

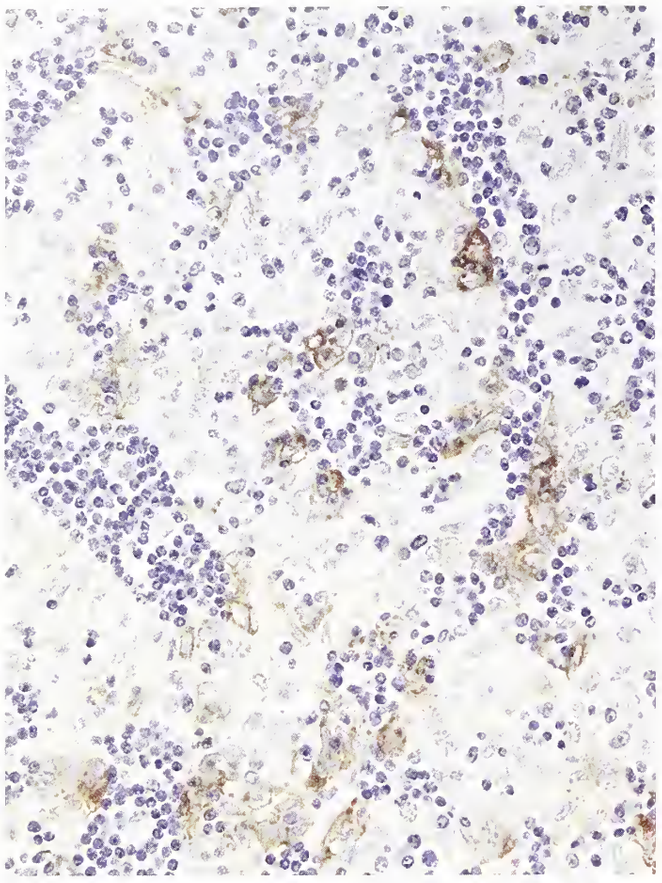


Figure 3-79
THYMOMA, MIXED LYMPHOCYTIC AND EPITHELIAL TYPE

Epithelial cells with CD57-positive reaction products in the cytoplasm are scattered, but many are nonreactive. (Immunostaining for CD57)

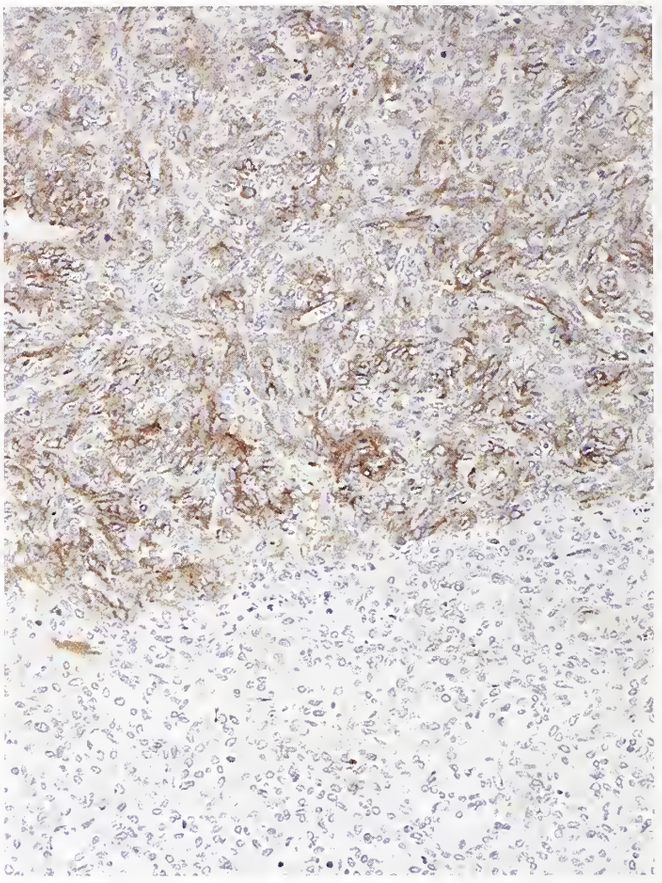


Figure 3-80
THYMOMA, PREDOMINANTLY EPITHELIAL, SHORT SPINDLE CELL TYPE

Although the constituent cells are morphologically similar, half of the area contains strongly CD57-immunoreactive cells and the other half weakly or nonreactive cells (same case as that in figure 3-48). (Immunostaining for CD57)

be identified in almost all thymomas by our definition, unless the tumors consist almost entirely of epithelial cells. A good example is shown in figure 3-83, which demonstrates double-positive thymocytes surrounding areas of medullary differentiation containing single-positive thymocytes. CD1a-positive lymphocytes are numerous in lymphocyte predominant and mixed cell type thymoma, decrease in epithelial cell predominant thymoma, and cannot be detected in thymic carcinoma (98). Müller-Hermelink et al. (52,81) stated that some of what they call well-differentiated, organotypic thymic carcinoma contained immature (cortical) thymocytes. This statement is understandable, because well-differentiated (organotypic) thymic carcinoma is categorized by us into a group of atypical thymomas including active polygonal cell–predominant thymoma with increased proliferative activity. In other words, by our definition, thymoma retains the function of the thymus to attract immature T cells from the bone marrow to make them mature (98,99) whereas thymic carcinoma has lost this function. As a result, lymphocytes infiltrating thymic carcinoma are mature T cells, as seen in cancers of other organs. CD1a-positive immature (cortical) lymphocytes can be stained with MIC2 antibody 013 after formalin fixation, which has been used for diagnosing Ewing's sarcomas and peripheral primitive neuroectodermal tumors. Therefore, it can be used to confirm a diagnosis of thymoma in small biopsy specimens, to distinguish invasive thymoma and thymic carcinoma, and to classify thymic epithelial tumors (38a,40a). Anti-terminal deoxynucleotidyl transferase (TdT) antibody also can be applied to formalin-fixed paraffin-embedded sections (Table 1-3).

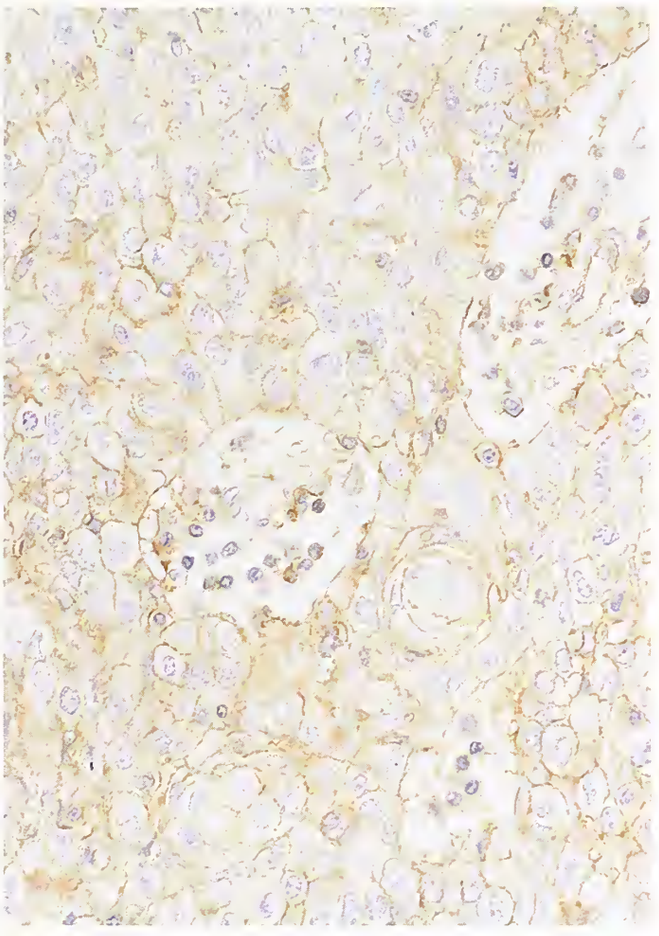


Figure 3-81
THYMOMA, PREDOMINANTLY EPITHELIAL, POLYGONAL CELL TYPE

Immunoreaction products are present in the cytoplasmic membrane of polygonal epithelial cells in a pleural implant, and small round cells in perivascular spaces. (Immunostaining for beta-2-microglobulin)

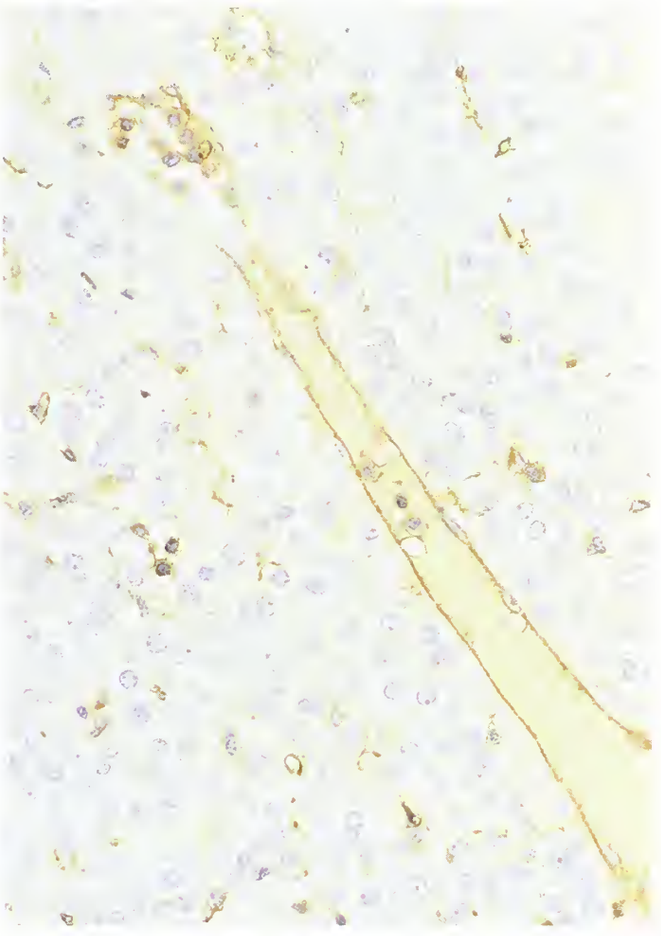


Figure 3-82
THYMOMA, PREDOMINANTLY EPITHELIAL. SHORT SPINDLE CELL TYPE

No or very weak reaction product for beta-2-microglobulin is noted in the short spindle epithelial cells (same case as that in figures 3-18, 3-48). (Immunostaining for beta-2-microglobulin)

In addition to T cells, areas of medullary differentiation contain CD20-positive B lymphocytes, thus mimicking the medulla of the normal thymus (39).

CD1a-negative and S-100 beta-positive interdigitating reticulum cells (Langerhans cells) are scattered in the parenchyma of thymoma and in nests of thymic carcinoma, but also appear as clusters in areas of thymoma showing medullary differentiation, as in the normal thymus (figs. 3-84, 3-85) (57).

Myoid cells, which are found in the fetal thymus of mammals including humans, and in a few thymomas, possess centrally located small nuclei and abundant cytoplasm containing eosinophilic fibrillar structures. Their cytoplasm immunostains by antibodies recognizing desmin, myoglobin, and muscle actin (fig. 3-86). No myoid cells have been found in thymic cancers examined so far except for sarcomatoid carcinoma with rhabdomyoblastic differentiation, an example of which was reported by Snover et al. (103).

Ultrastructural Findings. The ultrastructural architecture of the normal thymus, consisting of reticular epithelial cells with elongated cytoplasmic processes and lymphoid cells, is retained to various degrees in thymoma (50,66,67). The epithelial cells, characterized by bundles of tonofilaments in their cytoplasm and the presence of a large number of desmosomes, extend their fine cellular reticula within and around the parenchyma; the outer surface of epithelial cells is covered by a basement membrane (figs. 3-87, 3-88). In areas with epithelial cell predominance, solid cords

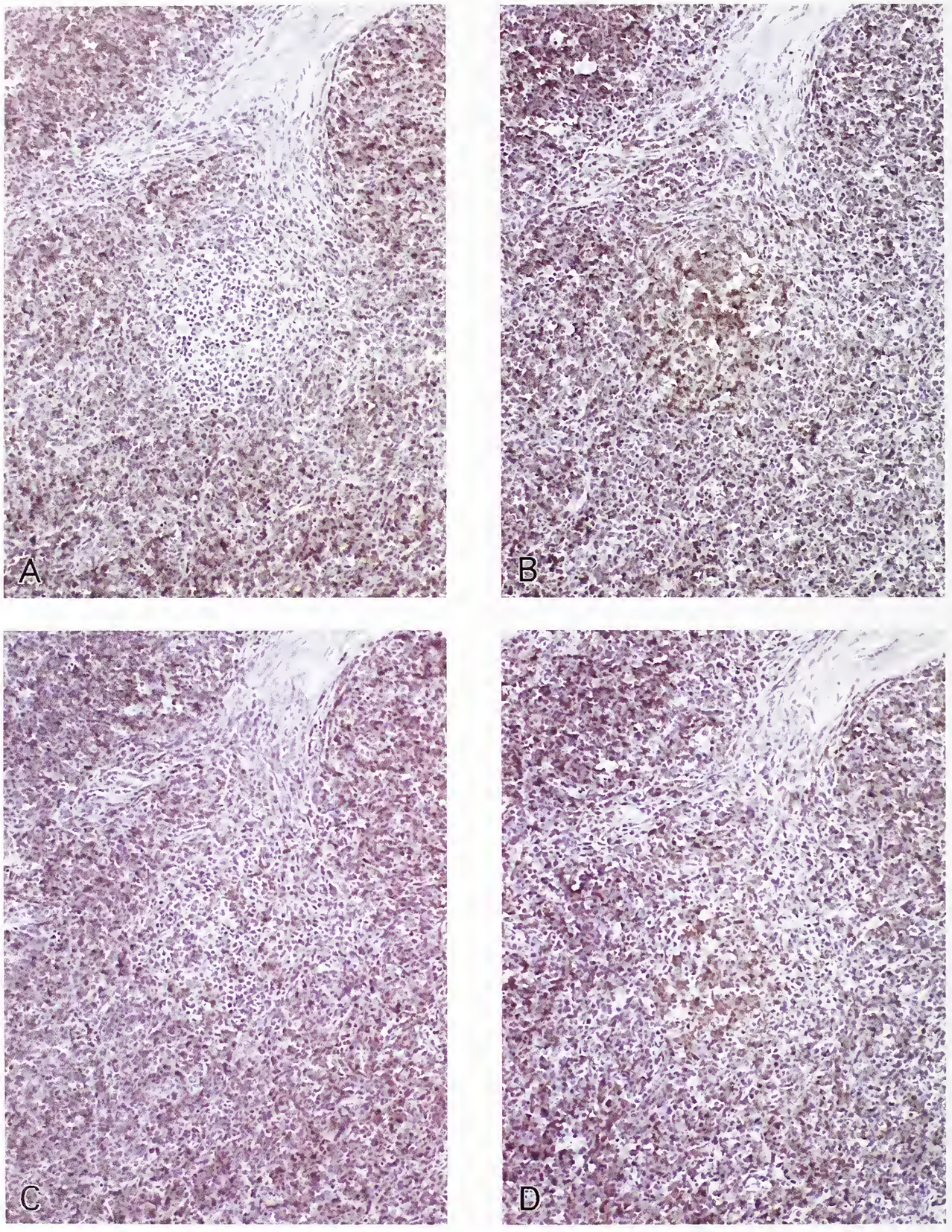


Figure 3-83
THYMOMA WITH MEDULLARY DIFFERENTIATION

Serial sections immunostained for surface markers of lymphocytes reveal that an area of medullary differentiation in the center of the photograph is composed of: A, cells nonreactive for CD1a; B, cells entirely immunoreactive for CD3; C, cells partly reactive and partly nonreactive for CD4; and D, cells partly reactive and partly nonreactive for CD8. Areas surrounding a focus of medullary differentiation consist of lymphocytes with a CD1a+, CD3+, CD4+, and CD8+ phenotype. (Immunostaining for lymphocytes markers: A, CD1a; B, CD3; C, CD4; D, CD8)

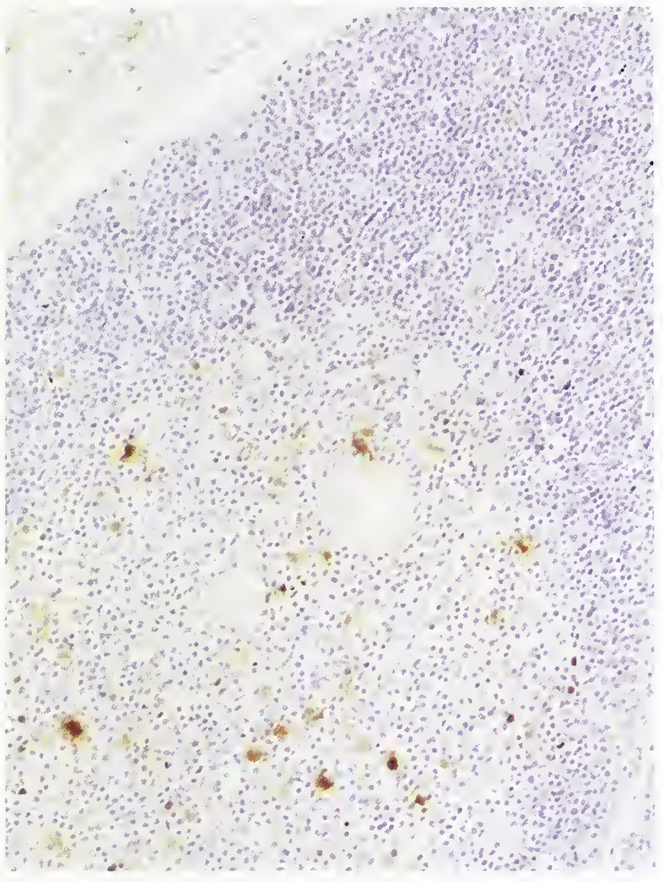


Figure 3-84
NORMAL THYMUS WITH INTERDIGITATING RETICULUM CELLS

Interdigitating reticulum cells positive for S-100 protein are almost entirely confined to within the medulla. (Immunostaining for S-100 beta)

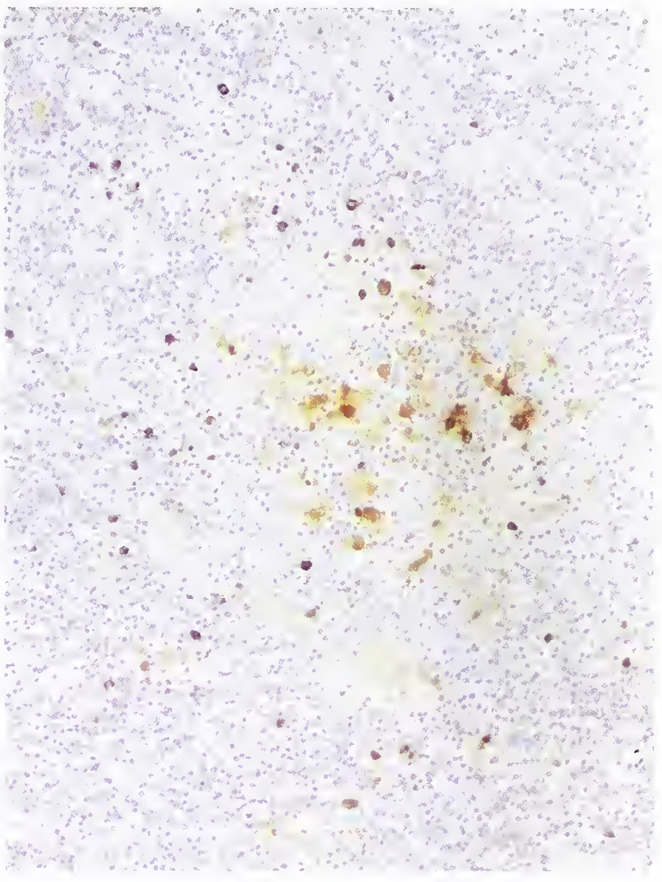


Figure 3-85
THYMOMA, LYMPHOCYTE-PREDOMINANT TYPE, WITH INTERDIGITATING RETICULUM CELLS

An area of medullary differentiation is studded with interdigitating reticulum cells showing an irregular outline, and some cytoplasmic processes whose cytoplasm is stained for S-100 beta protein. (Immunostaining for S-100 beta)

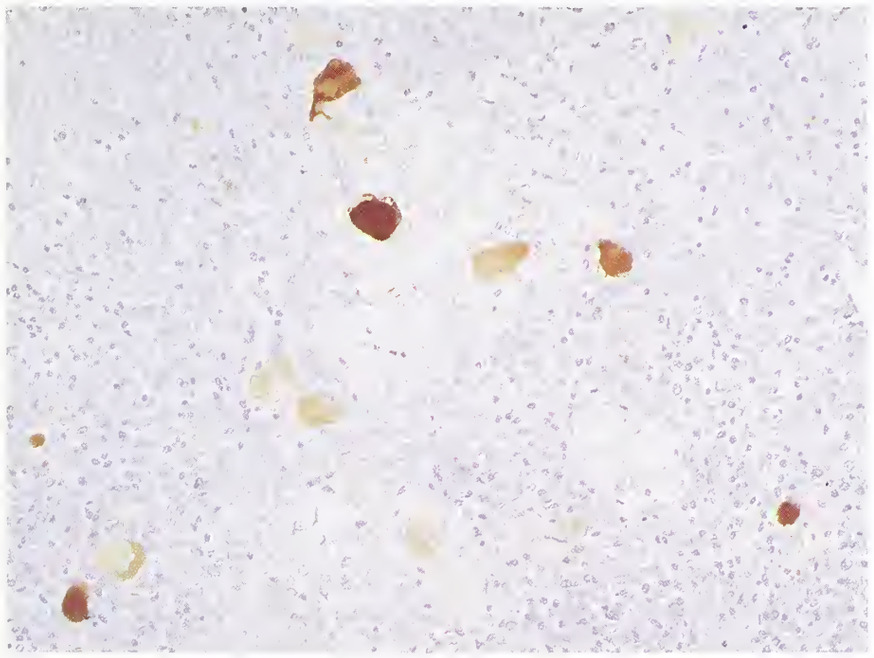


Figure 3-86
THYMOMA WITH MYOID CELLS

Scattered in mixed lymphocytic and epithelial thymoma are large cells with abundant cytoplasm stained intensely for myoglobin. (Immunostaining for myoglobin)

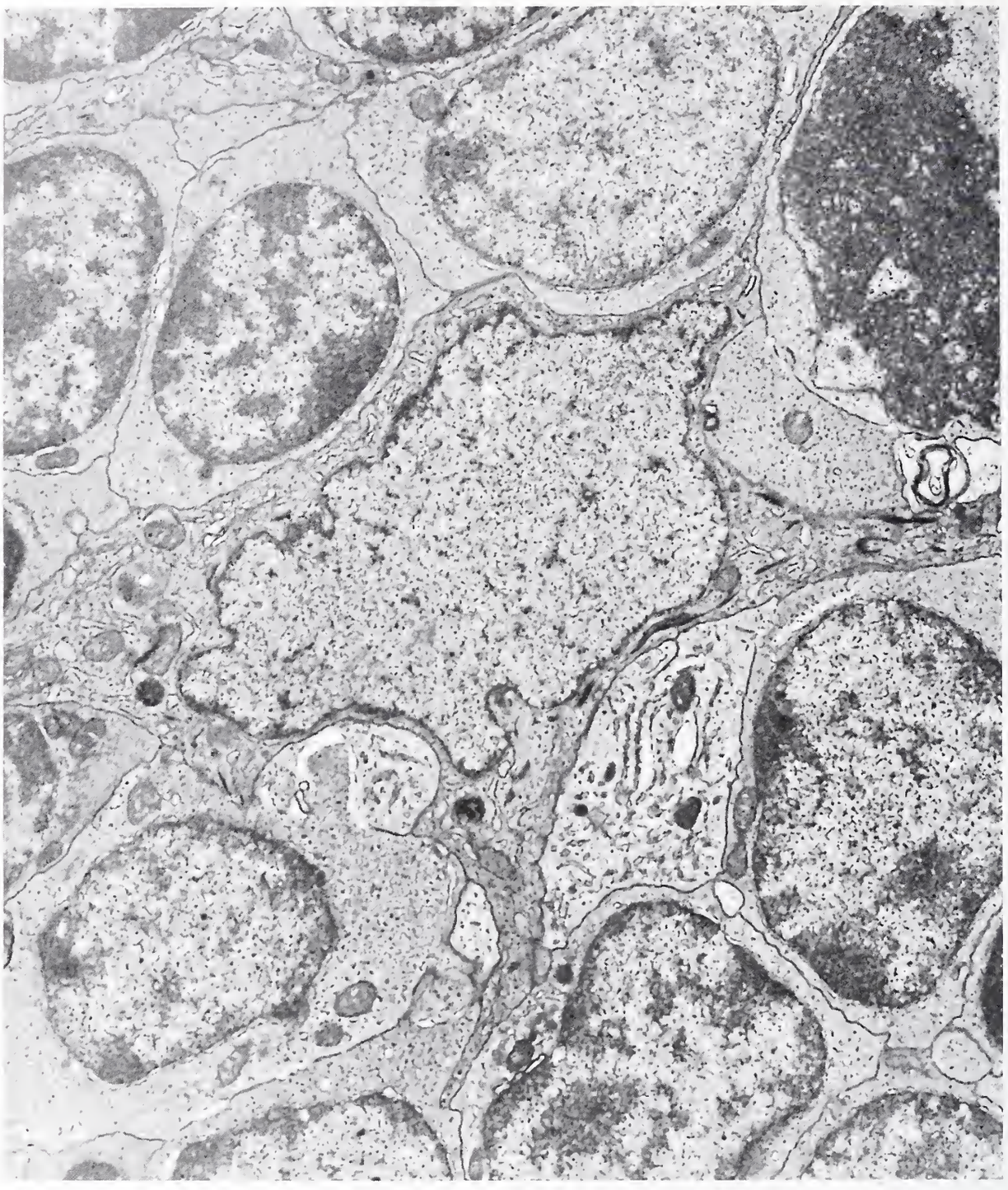


Figure 3-87
ULTRASTRUCTURE OF THYMOMA
The epithelial cells in the center have elongated cell processes and tonofilaments. A lymphocyte mitosis is seen at the upper right in close association with an epithelial cell process (X8,000). (Fig. 92 from Fascicle 13, 2nd Series.)

and nests are formed instead of extensions of slender epithelial reticula. Keratinization is seen in areas corresponding to Hassall corpuscles by light microscopy. Spindle cells can also be identified as epithelial in nature from the presence of desmosomes and intracytoplasmic tonofilaments (65). Other cytoplasmic organelles include a moderate number of mitochondria, a well-developed Golgi apparatus, a scanty rough endoplasmic reticulum, lysosomes, and occasional lipid droplets. The nuclei of epithelial cells of thymoma are oval or irregularly indented, with

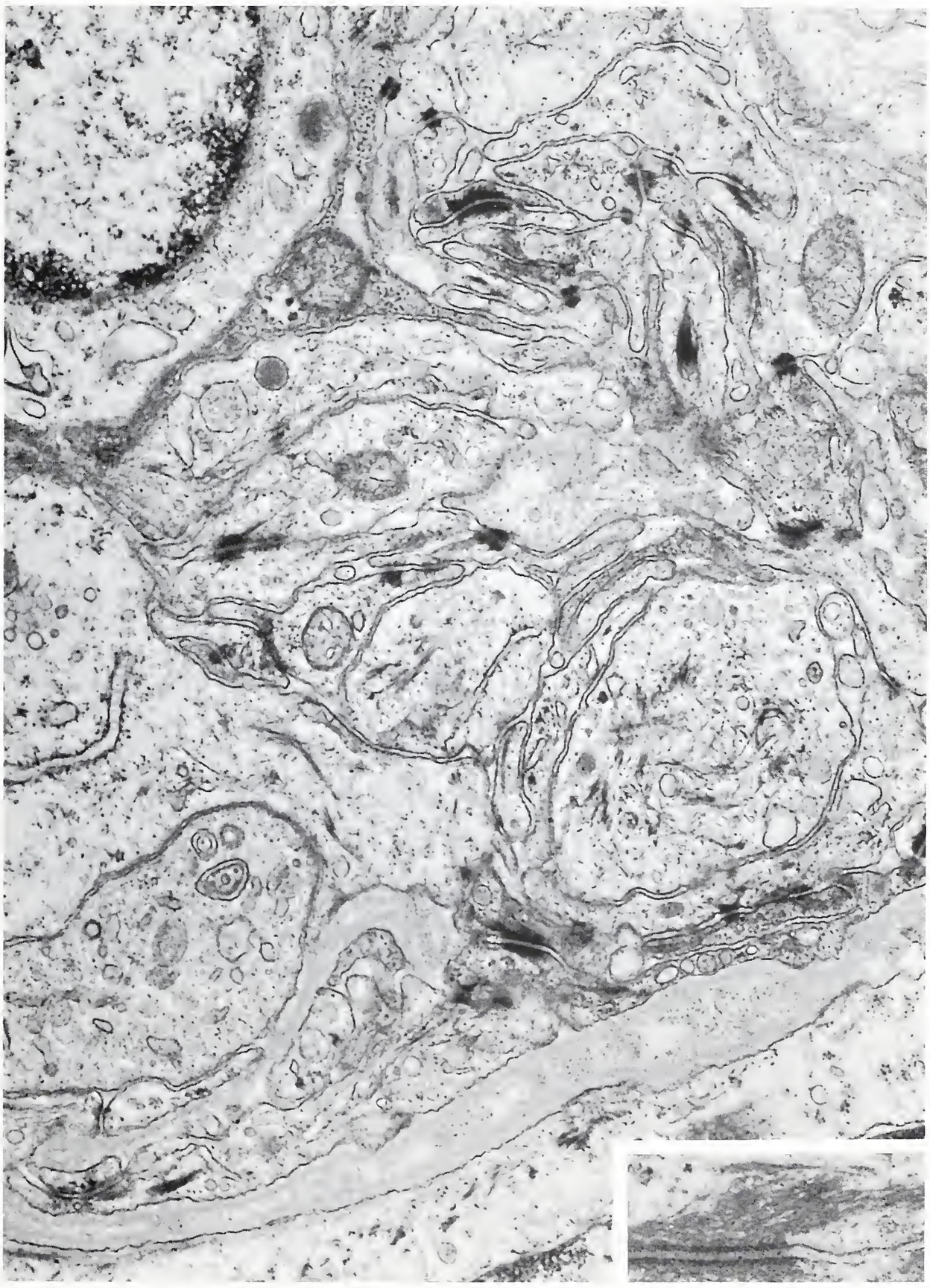


Figure 3-88
ULTRASTRUCTURE OF THYMOMA

Complex cellular interdigitations, many desmosomes, and a basal lamina characterize this area of thymoma (X20,000). Inset: Tonofilaments inserted into a typical desmosome (X40,000). (Fig. 93 from Fascicle 13, 2nd Series.)

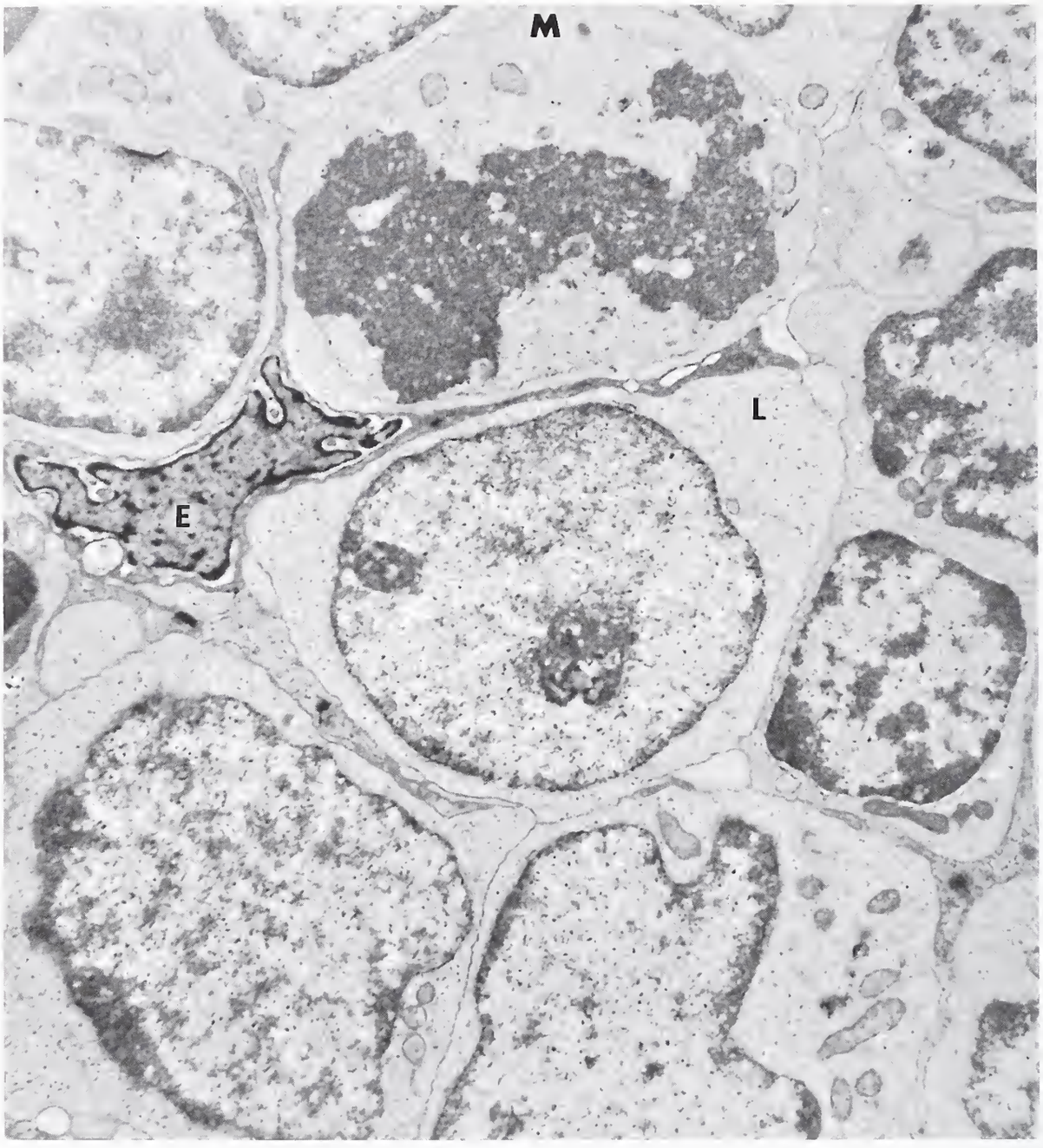


Figure 3-89
ULTRASTRUCTURE OF THYMOMA

Seen is an epithelial cell (E) with attenuated processes, an electron-dense nucleus, and cytoplasm. Lymphocyte activation is manifested by the presence of scant heterochromatin and nucleolar prominence (L). One of the lymphocytes is undergoing mitosis (M). Mature and inactive lymphocytes are also present (X8,000). (Fig. 99 from Fascicle 13, 2nd Series.)

condensed heterochromatin beneath the nuclear membrane and various-sized nucleoli. Basement membranes are irregularly interspersed between tumor cells, although there is a tendency for the basement membrane to surround clusters of tumor cells (fig. 3-88).

Thymic lymphocytes (thymocytes) are characterized by smooth cytoplasmic borders, oval dark nuclei, and a paucity of cytoplasmic organelles. Mature (or medullary) lymphocytes in the resting phase are small with nuclei containing abundant heterochromatin, whereas activated (cortical) lymphocytes are larger and have nuclei showing scanty heterochromatin, nucleolar prominence, and an increased number of cytoplasmic polyribosomes. Mitotic figures can be observed (fig. 3-89).

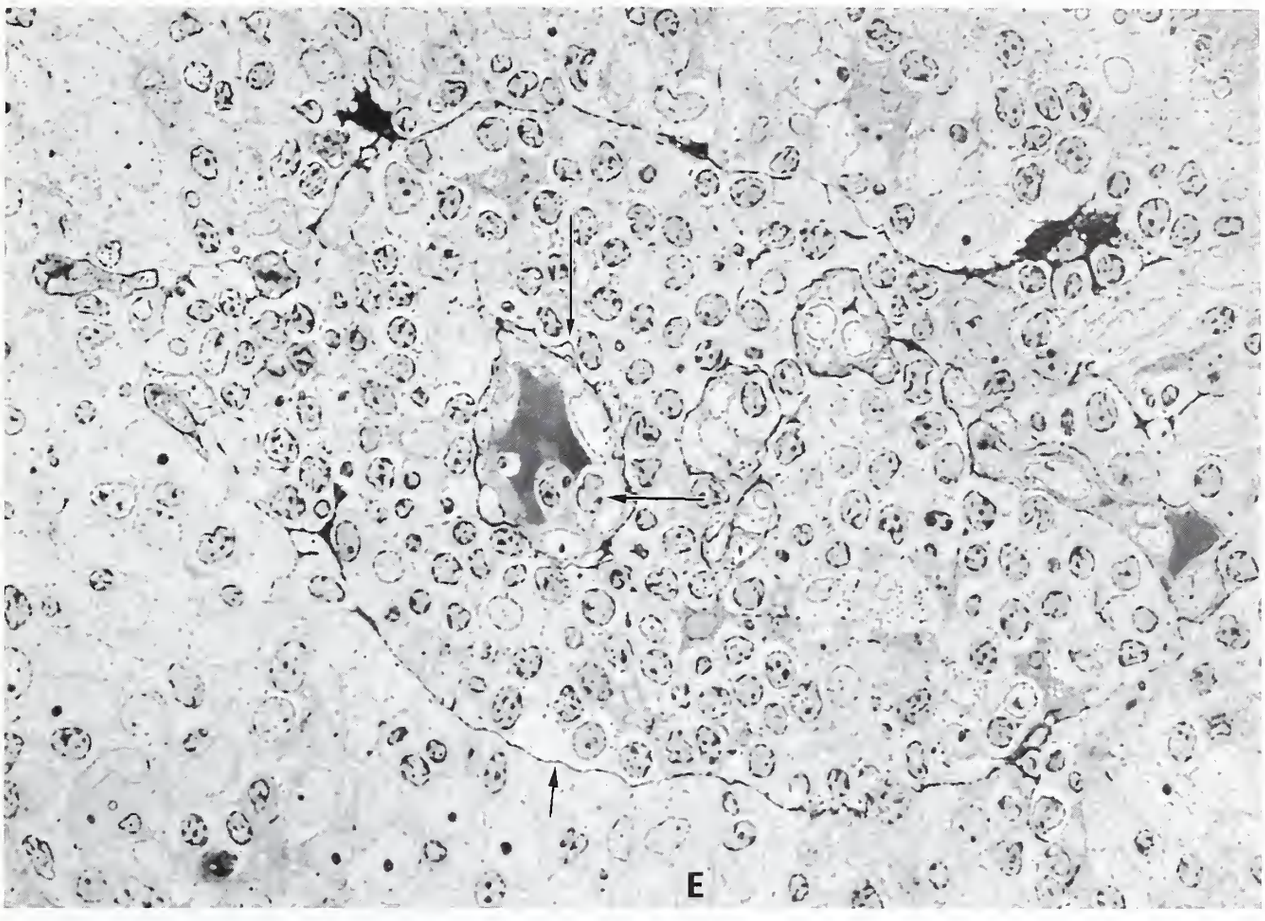


Figure 3-90
ULTRASTRUCTURE OF THYMOMA

This shows a typical perivascular space with a central vessel and branches, endothelial lamina (downward arrow), a lymphocyte-packed space, epithelial lamina (upward arrow), and palisading epithelial cells (E). The horizontal arrow indicates a lymphocyte within an endothelial cell (X650). (Fig. 105 from Fascicle 13, 2nd Series.)

Perivascular spaces are frequently dilated, and contain amorphous material, lymphocytes, mast cells, macrophages, and collagen. Both vascular and epithelial basement membranes are observed (figs. 3-90, 3-91).

Gland-like spaces are lined by epithelial cells, with tonofibrils and microvilli at the free cell surface. Junctional complexes are observed at the cell borders near the free cell surface.

Levine et al. (67) described a form of emperipolesis in thymoma, that is, the presence of degenerating lymphocytes in a space encompassed by epithelial cytoplasm. However, the epithelial cells have no signs of degeneration. In the end-stage of this process, spaces in the epithelial cells contain myelin figures and other cellular debris.

Myoid cells, which may be present in thymomas, are characterized by numerous sarcomeres and Z-bands (see fig. 3-72). Epithelial cells filled with mucus granules may be found, as well as spaces containing amorphous material; the spaces are lined by epithelial cells equipped with microvilli.

Although thymoma is ultrastructurally characteristic, electron microscopic studies are not common in routine practice since diagnosis by immunohistochemical methods is much easier.

Conditions and Diseases Associated with Thymoma. The most common paraneoplastic phenomenon associated with thymoma is myasthenia gravis, which affects one third to half of all thymoma patients. According to Lewis et al. (68), of 283 patients with thymoma treated at the Mayo Clinic during a 40-year period, 130 (46 percent) had myasthenia gravis. Nonmyasthenic paraneoplastic phenomena were present in 28 patients (10 percent), 10 of whom had myasthenia in combination. Eleven patients had hematologic

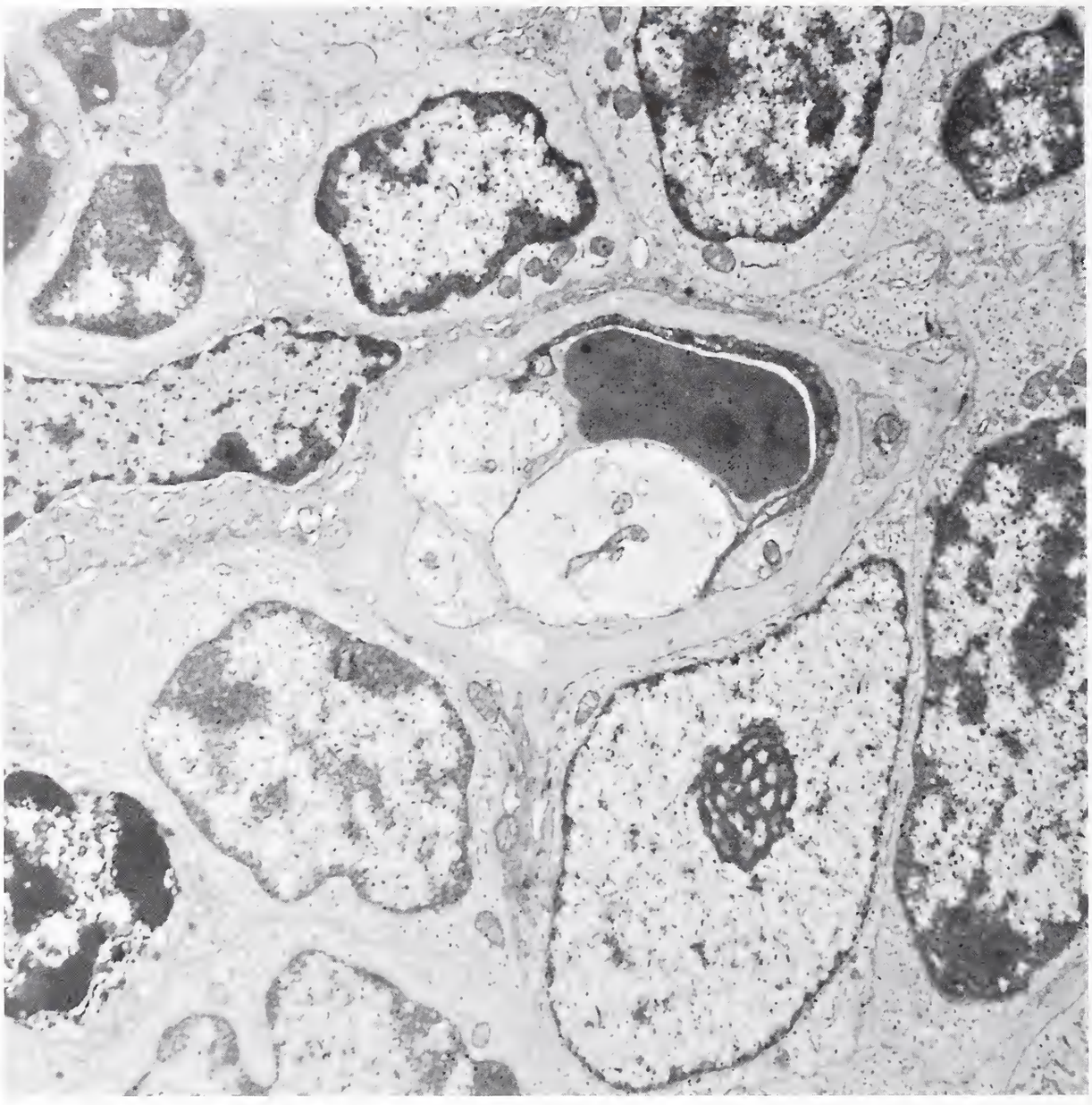


Figure 3-91
ULTRASTRUCTURE OF THYMOMA

The central vessel of a thymoma is completely surrounded by epithelial cell processes. Basal laminae of both the vessel and epithelial cells are well defined. A well-developed nucleolonema is present in the epithelial cell below the vessel (X8,000). (Fig. 103 from Fascicle 13, 2nd Series.)

disorders: hypogammaglobulinemia (5 patients), pure red cell aplasia (2 patients), and aplastic anemia (4 patients). Fifteen had possible autoimmune-related disorders: pernicious anemia (3 patients), a positive lupus erythematosis (LE) preparation (3 patients), polymyositis (2 patients); one patient had each of the following: keratoconjunctivitis sicca, alopecia areata, mixed collagen-vascular disease, Graves' disease, Crohn's disease, chronic ulcerative colitis, anhydrosis/orthostasis, and positivity for rheumatoid factor. Myocarditis and myopathy were seen in one patient each. Forty-eight patients (17 percent) had another primary tumor.

Myasthenia gravis is associated with predominantly lymphocytic thymomas (62,73), but several reports have shown a similar distribution of histologic subtypes in both myasthenic and nonmyasthenic patients (68,95). In our series, myasthenia gravis was a complication in 11 of 79 thymomas (13.9 percent), of which 9 were of the polygonal cell type and 2 were of the mixed polygonal and

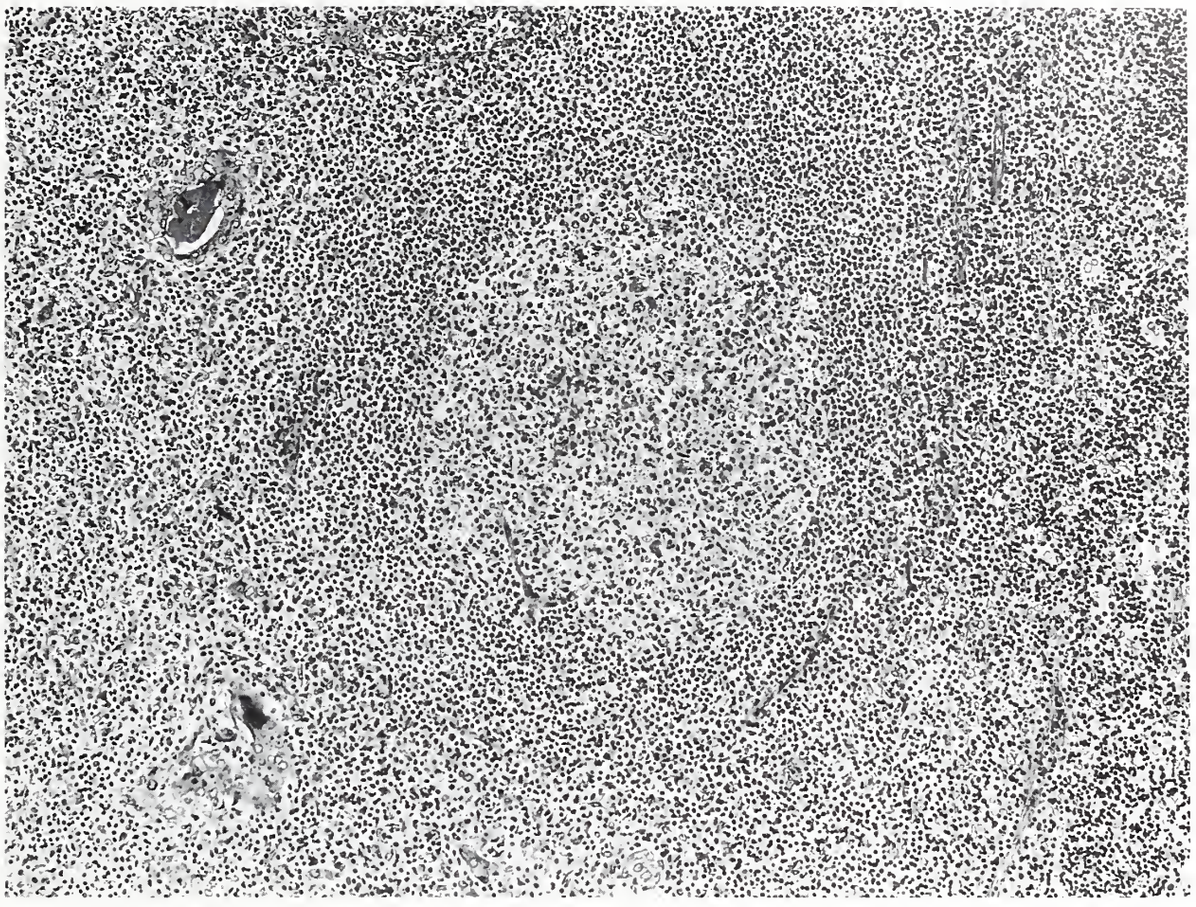


Figure 3-92
THYMOMA WITH LYMPH FOLLICLE WITH GERMINAL CENTER
A lymph follicle with a prominent germinal center is present within a lymphocyte predominant thymoma, which also contains Hassall-like bodies. Residual thymus also contained lymph follicles with germinal centers.

spindle cell type; none of the pure spindle cell type was complicated by myasthenia gravis (56).

According to Kirchner et al. (53), association of myasthenia gravis was highest in well-differentiated thymic carcinoma (77 percent), followed by cortical thymoma (66 percent) and other subtypes of thymoma (33 to 39 percent); no other type of thymic carcinoma was associated with myasthenia gravis. About half of the patients with myasthenia gravis show lymph follicles with germinal centers in the residual thymus, whereas only a few nonmyasthenia patients do so (92); in those cases, lymph follicles with germinal centers are often seen within thymoma tissue (fig. 3-92).

In spite of the frequent association of myasthenia gravis with thymoma, the causal relationship between the two conditions is not yet understood. However, it is known that myasthenia gravis is an autoimmune disease affecting the acetylcholine receptor at the neuromuscular junction, and production of autoantibody against the acetylcholine receptor alpha-subunit is assumed to be the cause of myasthenia gravis (64). The source of acetylcholine receptors in the thymus is considered to be myoid cells present in the medullae of the thymus.

Marx et al. (70a) identified neurofilaments and titin-like epitope expressed aberrantly in many neoplastic epithelial cells of thymic epithelial tumors with cortical differentiation, including the cortical thymomas and well-differentiated thymic carcinomas of Kirchner et al. (53). They suggested that their abnormal expression in thymomas might trigger anti-titin autoimmunity for pathogenesis of myasthenia gravis.

Many reports have described the presence of myasthenia gravis as an indicator of poor prognosis (34,63,95). However, recent studies by Wilkins and Castleman (111), Maggi et al. (69), and Lewis et al. (68) have not supported this concept,

and patients with myasthenia gravis have been shown to have a survival rate equal to that of patients with nonmyasthenia-related thymoma. These authors attributed the equal prognosis to better postoperative respiratory support as well as improved long-term medical care of myasthenic patients. Monden and associates (73) found that thymoma was detected earlier, recurrence rate was lower, and the survival curve better in the group with myasthenia gravis.

Spindle cell thymoma has been noted to occur more frequently in patients with hypogammaglobulinemia (91), pure red cell aplasia, and aplastic anemia. All of 17 cases of thymoma associated with pure red cell aplasia collected by Masaoka et al. (71) were of the spindle cell type with a variable lymphocyte component; 2 were associated with myasthenia gravis and 3 with hypogammaglobulinemia. The Coombs and antinuclear antibody tests were positive in 5 cases. Thymic tissue attached to thymoma displayed epithelial clusters frequently (10 out of 11 cases) but no germinal centers, and could well be a bud of another thymoma. In a series of Lewis et al. (68), only 3 of 11 patients with hematologic abnormalities had spindle cell tumors.

Hematologic disorders are associated less frequently with thymoma than myasthenia gravis, and are studied less. Pure red cell aplasia occurs in only 5 percent of thymoma patients, and thymomas are found in 50 percent of patients with pure red cell aplasia (93). Pure red cell aplasia is divided into that without any suspected cause or drug induction and that with some suspected cause. The aplasia associated with thymoma is chronic and of the latter category; also in this category are malignant lymphoma, chronic leukemia, systemic lupus erythematosus, and Sjögren's syndrome. Pure red cell aplasia can be caused by any factors that inhibit the process of erythroid cell maturation from totipotent stem cells (CFU-S) to erythrocytes through the erythroid burst-forming unit (BFU-E) and erythroid colony-forming unit (CFU-E). In this process, various factors are known to be involved, such as interleukin 3 and erythropoietin. Not only autoantibodies against progenitor cells of the erythroid series and factors that enhance erythropoiesis, but also factors that inhibit erythropoiesis, such as suppressor T cells and gamma-interferon, can cause pure red cell aplasia (71). In Masaoka's cases, highly positive Coombs and antinuclear antibody tests, and a decrease of the CD4/CD8 ratio were noted, suggesting involvement of other autoimmune diseases and activation of suppressor T cells.

Pure red cell aplasia occurs either concomitantly with detection of thymoma or after treatment of thymoma, although the latter situation is rare; thymectomy with resection of thymoma is effective treatment in 20 to 40 percent of cases. Steroid therapy is also instituted in many cases, sometimes with immunosuppressive agents. The role of thymoma in the occurrence of pure red cell aplasia is unknown at present, but suggested explanations are: 1) thymoma shares an antigen in common with cells of the erythroid series; 2) overproduction of suppressor T cells by thymoma, at times producing not only pure red cell aplasia but also hypogammaglobulinemia; and 3) both thymoma and pure red cell aplasia occur through the action of a common causative agent (71).

Although agents causing thymoma are not known, and though it does not appear to be associated with Epstein-Barr virus (see Thymic Carcinoma), a case of thymoma was reported in a pedigree of Li-Fraumeni syndrome (unpublished data, H. Sugimura, Hamamatsu, Japan, 1994). Tumors reported in this pedigree were carcinoma of the adrenal cortex, astrocytoma, hepatoblastoma, and carcinoma of the pancreas. The patient who developed thymoma was a 19-year-old male student and a carrier of the p53 germline mutation (exon 8). (The patient is family 2, III-5, in reference 96.) The surgically resected tumor was 9.5 x 6.0 x 3.7 cm, weighed 100 g, and was of predominantly lymphocytic, polygonal cell type thymoma with no cellular atypia (cortical thymoma). Immunohistochemically, p53 product accumulated in the nuclei of the epithelial cells, but loss of heterozygosity in tumor cells was not detected. Occurrence of thymoma in a pedigree of Li-Fraumeni syndrome may be contingent, but a genetic approach not only determines etiology but is also important for evaluation of the degree of malignancy.

Factors Associated with Degree of Malignancy. Problems related to the assessment of the prognosis of patients with thymoma have been reviewed and described concisely and pertinently by Wick (109), who believes that staging procedures predicated on the degree of tumor invasion are still the best prognosticators for thymoma.

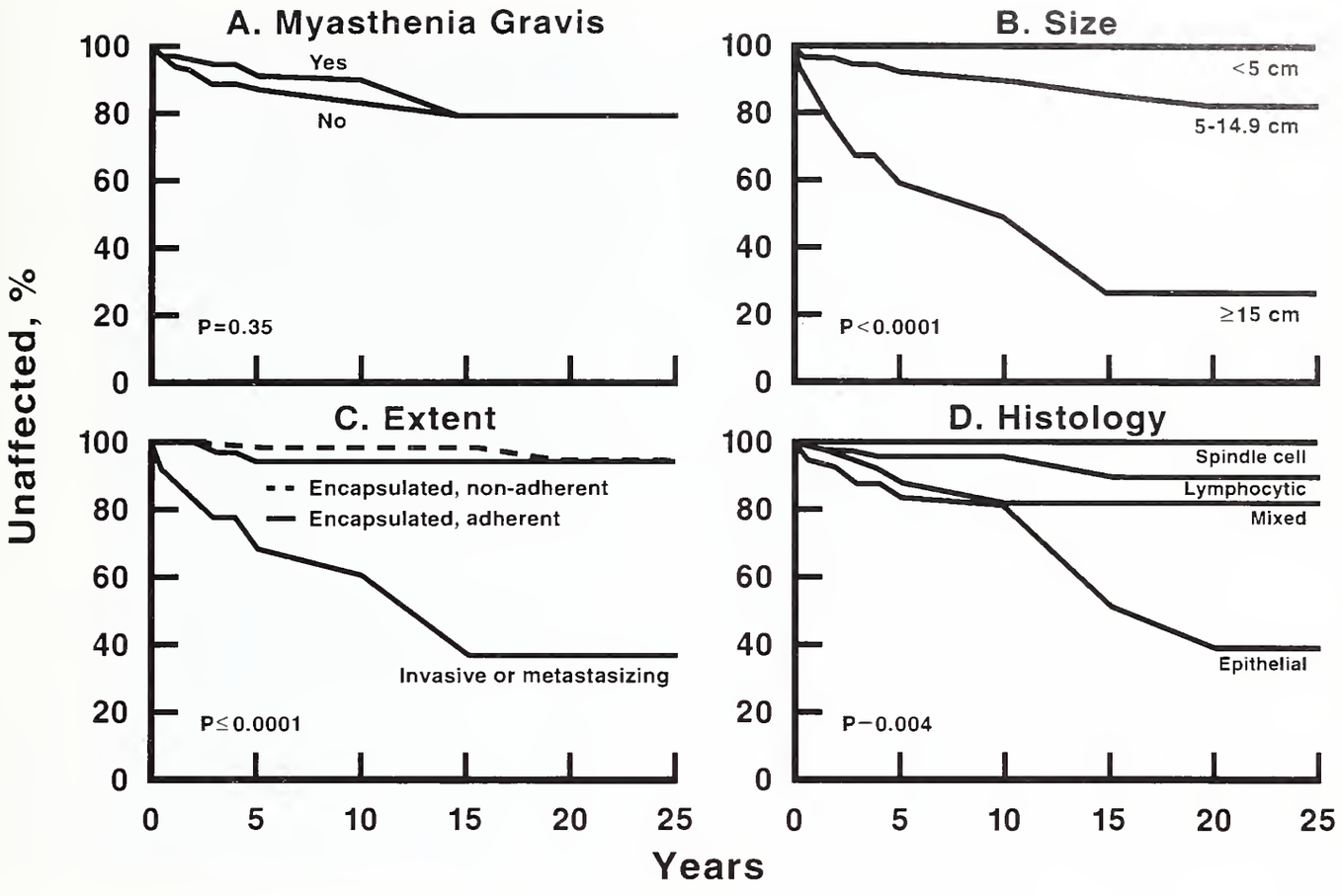


Figure 3-93
REPRESENTATIVE CURVES FOR SURVIVAL TO THYMOMA DEATH ACCORDING TO SELECTED VARIABLES
(Fig. 12 from Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma: a clinicopathologic review. Cancer 1987;60:2727–43.)

Recent studies at Memorial Sloan-Kettering Cancer Center also indicated that stage of the disease was the only independent prognostic factor affecting recurrence. Multivariate analysis showed that stage, tumor size, histology, and extent of surgical resection were independent predictors of long-term survival (35a).

Pathologists and clinicians agree that no histologic difference exists between encapsulated, surgically curable thymoma and invasive thymoma with an unfavorable outcome. This appears to be generally true, but spindle cell thymoma is considered to be practically a benign tumor and Müller-Hermelink and associates (70) include not only the medullary type but also the mixed cell type (mixed medullary and cortical type) in this category. The incidence of predominantly epithelial and polygonal cell type thymoma of clinical stage IV is high, and a majority of fatal cases are either predominantly epithelial polygonal cell type or mixed lymphocytic and polygonal epithelial cell type; the prognosis of patients with the spindle cell type is much better than for those with other subtypes of thymoma (Table 3-4; fig. 3-93) (68). Therefore, thymoma of the polygonal cell type, particularly the predominantly epithelial cell type, can be said to be more aggressive biologically than other cell types or histologic subtypes.

Epithelial cells of thymomas that show nuclear atypia are almost always of the polygonal cell type. The nuclei are large, round, and vesicular, and often contain distinct nucleoli; occasionally, mitotic figures are frequent (see fig. 3-51). The epithelial cells may have epidermoid features, and such tumors are categorized by Müller-Hermelink and associates (70) as well-differentiated (organotypical) carcinoma since they are more aggressive than thymomas of other subtypes (see figs. 3-47, 3-58).

In a study by Kirchner et al. (53), all medullary thymomas (6 cases) and mixed medullary

and cortical thymomas (27 cases) were of either stage I or II of Masaoka's classification; 12 percent of predominantly cortical thymomas (9 cases) were of stage III and none of stage IV; 38 percent and 9 percent of cortical thymomas (57 cases) were of stages III and IV, respectively; and 57 percent and 26 percent of well-differentiated thymic carcinomas (23 cases) were of stages III and IV, respectively.

Recently, Quintanilla-Martinez et al. (89) studied 116 patients with thymic epithelial tumors classified according to the proposals of Marino and Müller-Hermelink, and Kirchner et al. (53,70). They concluded that "their histologic classification has prognostic significance independent of tumor stage; medullary and mixed thymomas were benign tumors with no risk of recurrence; organoid (predominantly cortical) and cortical thymoma showed intermediate invasiveness and a low but significant risk of late relapse; and well-differentiated thymic carcinomas were always invasive and had a significantly increased risk of relapse and death" (fig. 3-94).

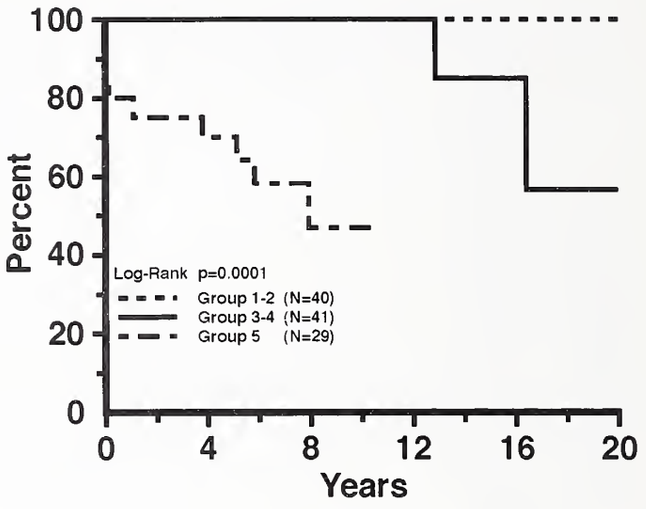


Figure 3-94
DISEASE-FREE SURVIVAL: FREEDOM FROM RELAPSE OF THYMIC EPITHELIAL TUMOR BY HISTOLOGY SUBTYPE

Group 1: medullary; group 2: mixed; group 3: organoid; group 4: cortical; and group 5: well-differentiated carcinoma (WDTC). Patients with WDTC relapsed more often and earlier than patients with other histologic types. (Fig. 2 from Quintanilla-Martinez L, Wilkins EW Jr, Choi N, Efird J, Hug E, Harris NL. Thymoma. Histologic subclassification is an independent prognostic factor. Cancer 1994;74:606–17.)

While accepting the merits of the Müller-Hermelink system, particularly with regard to some clinical features such as stage of disease and presence of myasthenia gravis, Pan et al. (84) reported that "further subclassification of cortical thymomas into organoid thymoma, conventional cortical thymoma, and well-differentiated carcinoma did not provide more information about clinical behavior, that by actuarial survival analyses none of the epithelial subtypes displayed a statistically significant influence on prognosis, and that staging remains the most important factor affecting the patient's outcome." Pescarmona et al. (86) proposed a model for clinicopathologic staging consisting of three major prognostic groups, based on both clinical stage and histologic types (cortical, medullary, and mixed), the validity of which has been supported by multivariate analysis.

As already mentioned, investigators employing the classifications of Marino and Müller-Hermelink, and Kirchner et al. reported that medullary and mixed thymomas are benign. However, two of our cases revealed hematogenous multiple lung metastases. The first case was a 58-year-old female who underwent resection of a 10 cm thymoma weighing 180 g, which was invasive but confined to within the thymus (stage II). Histologically, the tumor was predominantly lymphocytic and the epithelial component was a mixture of polygonal and short spindle-shaped cells forming frequent rosette-like structures (see fig. 3-60). Blood vessel invasion was noted frequently (fig. 3-95). Three years after surgery, the patient was found to have three metastatic nodules in the left lung of up to 13 mm in diameter, which were resected. Histologically, they were similar to the primary tumor although the epithelial component predominated. The lung metastases were resected again 5 years later and the patient was alive with further lung metastases at the time of writing, 11 years after the first surgery. The second case was a 66-year-old male who underwent combined resection of the mediastinal tumor and left lower lobe of the lung. The mediastinal tumor, 12.5 cm in diameter, invaded the lung and pericardium. The resected lobe of the lung contained three metastatic nodules of up to 13 mm in diameter. Histologically both primary and metastatic tumors were similar, consisting of sheets of short spindle-shaped cells occasionally forming gland-like structures (fig. 3-96), quite similar to the

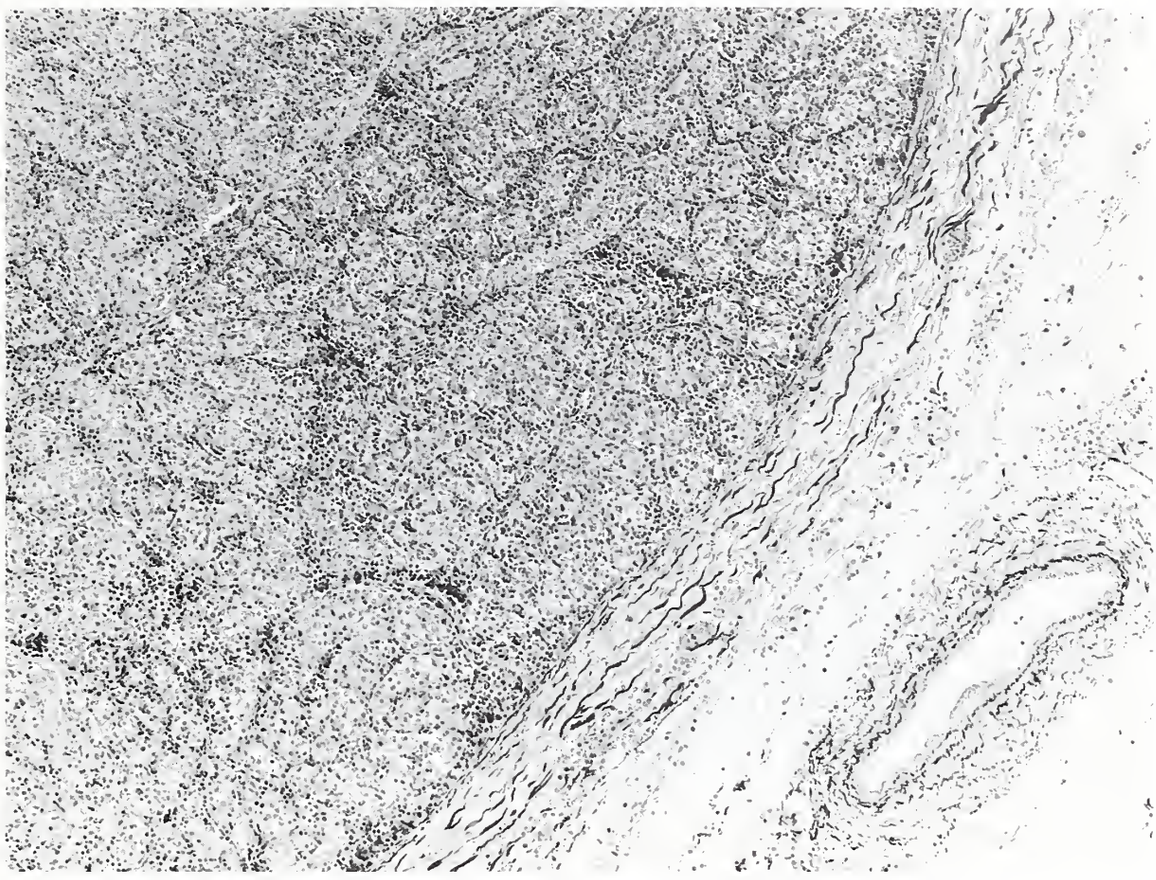


Figure 3-95
THYMOMA WITH BLOOD VESSEL INVASION

Thymoma of the mixed lymphocytic and epithelial cell type forming frequent rosette-like structures occludes a medium-sized vein. An artery is seen in the right lower corner (same case as that in figure 3-60). (Elastica stain)

features shown in figure 3-62. In this case, the tumor projected into the lumen of the innominate vein, which appeared to be covered by intact intima. Lung metastases were detected again 2 years after surgery, for which two courses of chemotherapy were given without effect, and the patient was alive with multiple lung metastases at the time of writing 5 years after surgery. In both cases no lymph node metastases were found (56).

The presence of such medullary thymomas indicates that short spindle-shaped or oval tumor cells showing rosettes and glandular structures may behave in a malignant fashion at times although growth is indolent, and may be biologically different from fibroblast-like spindle tumor cells.

Nomori et al. (83) measured the nuclear areas of epithelial cells of the normal thymus, hyperplastic thymus, and thymomas. They found that the nuclei of epithelial cells in thymoma were significantly larger than those of both normal and hyperplastic thymus, and that the nuclei of epithelial cells of invasive thymoma (clinical stages III and IV) were significantly larger ($47.4 \pm 6.7\ \mu m^2$) than those of noninvasive thymoma (clinical stages I and II; $36.5 \pm 7.5\ \mu m^2$). A similar study was carried out by Asamura et al. (33), who showed that the mean nuclear area increased significantly in increasing order from noninvasive thymoma to invasive thymoma to thymic carcinoma, ($49.27 \pm 7.88\ \mu m^2$, $62.44 \pm 5.10\ \mu m^2$, and $76.79 \pm 10.27\ \mu m^2$, respectively) (fig. 3-97). However, they also stated that there was a trend toward an increasing degree of malignancy from noninvasive to invasive thymoma. Thus, as there was a sizable overlap in the results obtained in the two groups, measurement of nuclear area is not satisfactory for predicting the behavior of individual cases of noninvasive and invasive thymoma.

At the same time, Asamura et al. (33) investigated the nuclear DNA content of noninvasive thymomas, invasive thymomas, and thymic carcinoma by cytofluorometry, and found that the

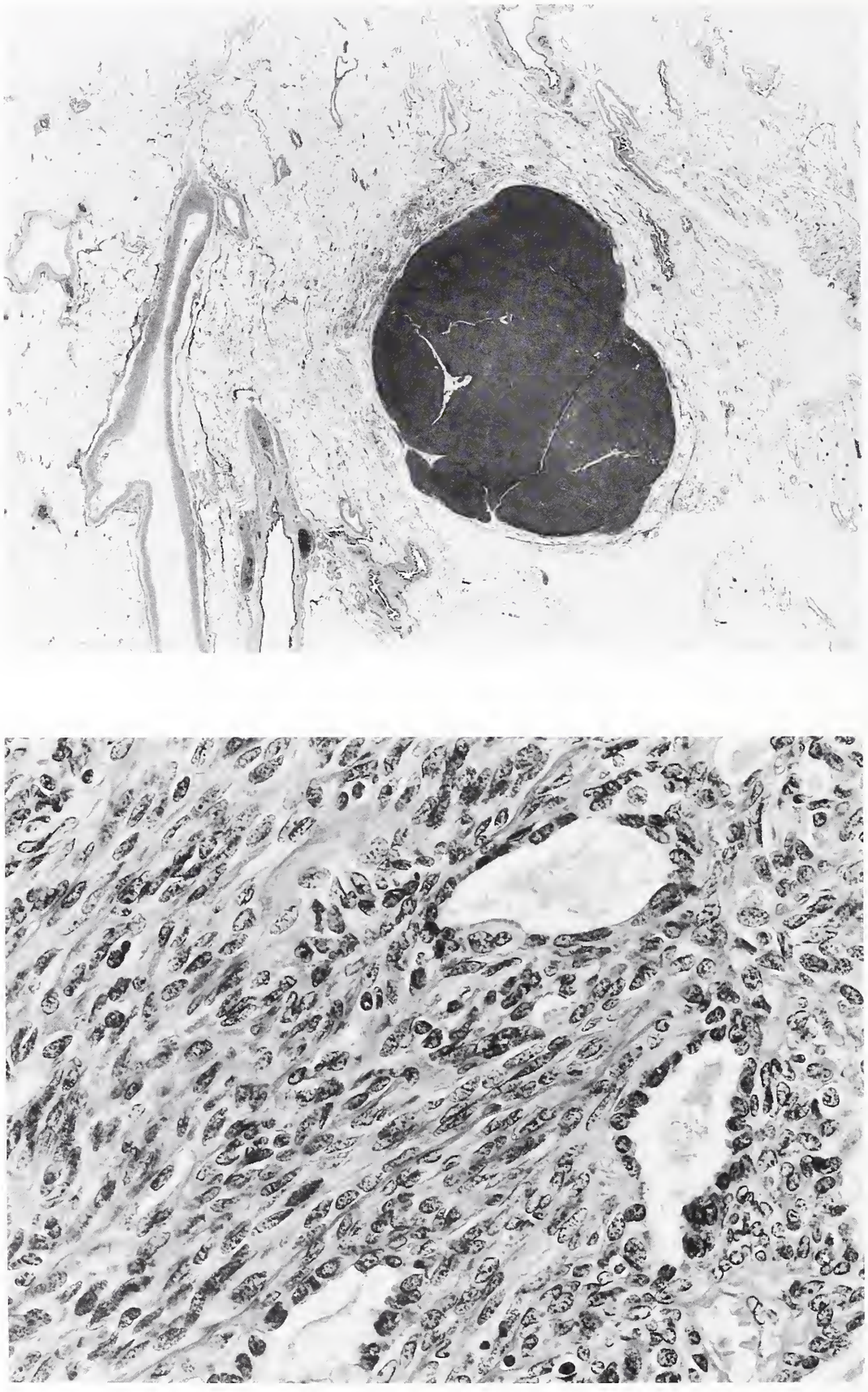


Figure 3-96
THYMOMA WITH GLAND FORMATION METASTATIC TO THE LUNG

Top: A small, well-defined, nonencapsulated tumor metastatic to the lung is shown.

Bottom: Higher magnification reveals glandular structures lined by cuboidal cells within a diffuse growth of oval to short spindle tumor cells.

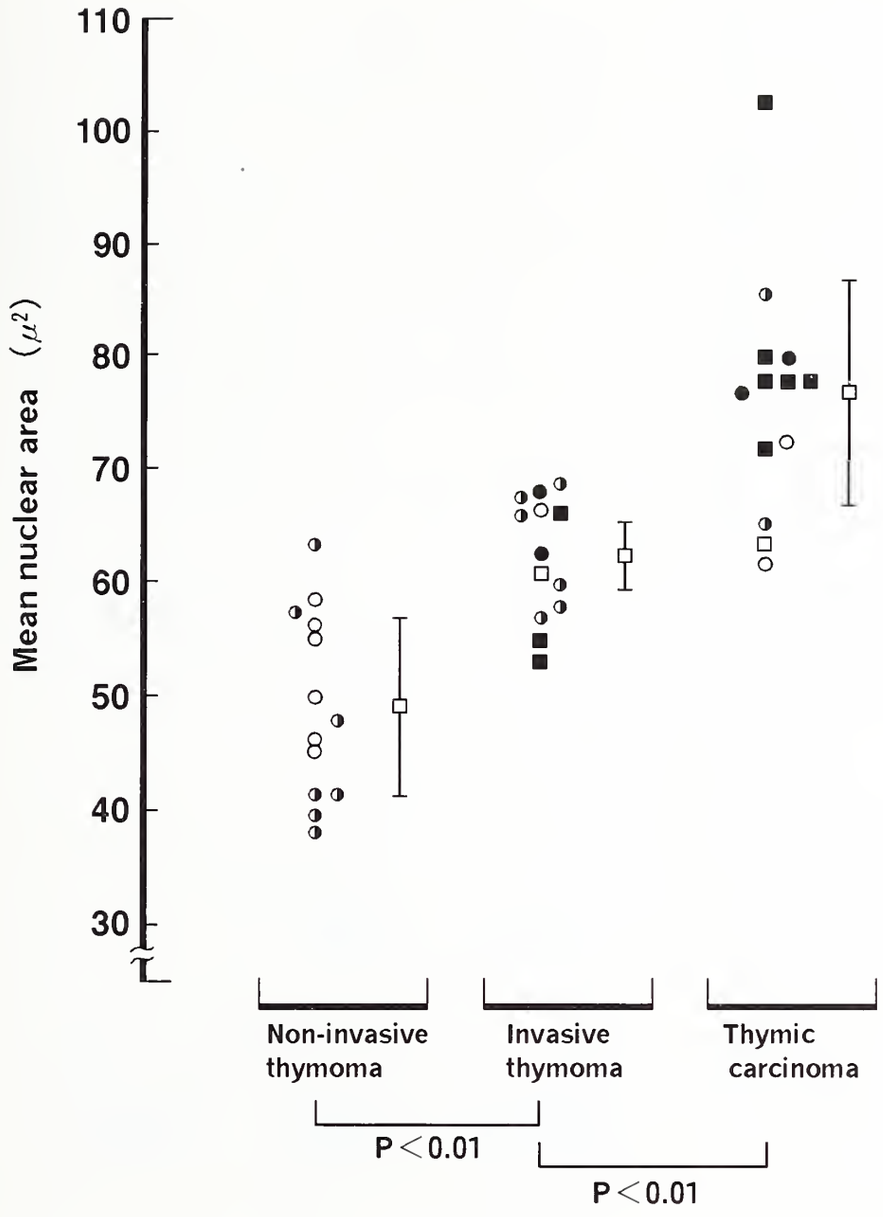


Figure 3-97
MEAN NUCLEAR AREAS OF NONINVASIVE THYMOMA, INVASIVE THYMOMA, AND THYMIC CARCINOMA
(Fig. 4 from Asamura H, Nakajima T, Mukai K, Noguchi M, Shimosato Y. Degree of malignancy of thymic epithelial tumors in terms of nuclear DNA content and nuclear area. Am J Pathol 1988;133:615–22.)

mean nuclear DNA content of thymic carcinoma was significantly higher than that of both invasive and noninvasive thymomas (3.82 ± 0.98C, 2.63 ± 0.28C, and 2.46 ± 0.18C, respectively); there was no significant difference between noninvasive and invasive thymoma (fig. 3-98). The aneuploid stem cell line appeared in 92.3 percent of thymic carcinomas, only one invasive thymoma (7.7 percent), and in no noninvasive thymomas. Abnormal DNA histogram patterns were seen in about half of all thymic carcinomas but in none of the thymomas. As with nuclear area, the overlap between noninvasive and invasive thymomas and between invasive thymoma and thymic carcinoma precludes using mean nuclear DNA content as a predictor of behavior in individual cases of thymoma. However, the three parameters, i.e., mean nuclear DNA content, the occurrence of an aneuploid stem cell line, and an abnormal DNA histogram pattern, are helpful for distinguishing invasive thymoma from thymic carcinoma.

Davies et al. (40) used flow cytometry to show that aneuploidy correlated with a more advanced stage of thymoma and occurred more frequently in epithelial-predominant thymoma; thus aneuploidy was predictive of tumor recurrence, independent of the effects of stage and histology. Kuo et al. (60), also using flow cytometry, reported that the DNA indices of grossly invasive thymoma and thymic carcinoma

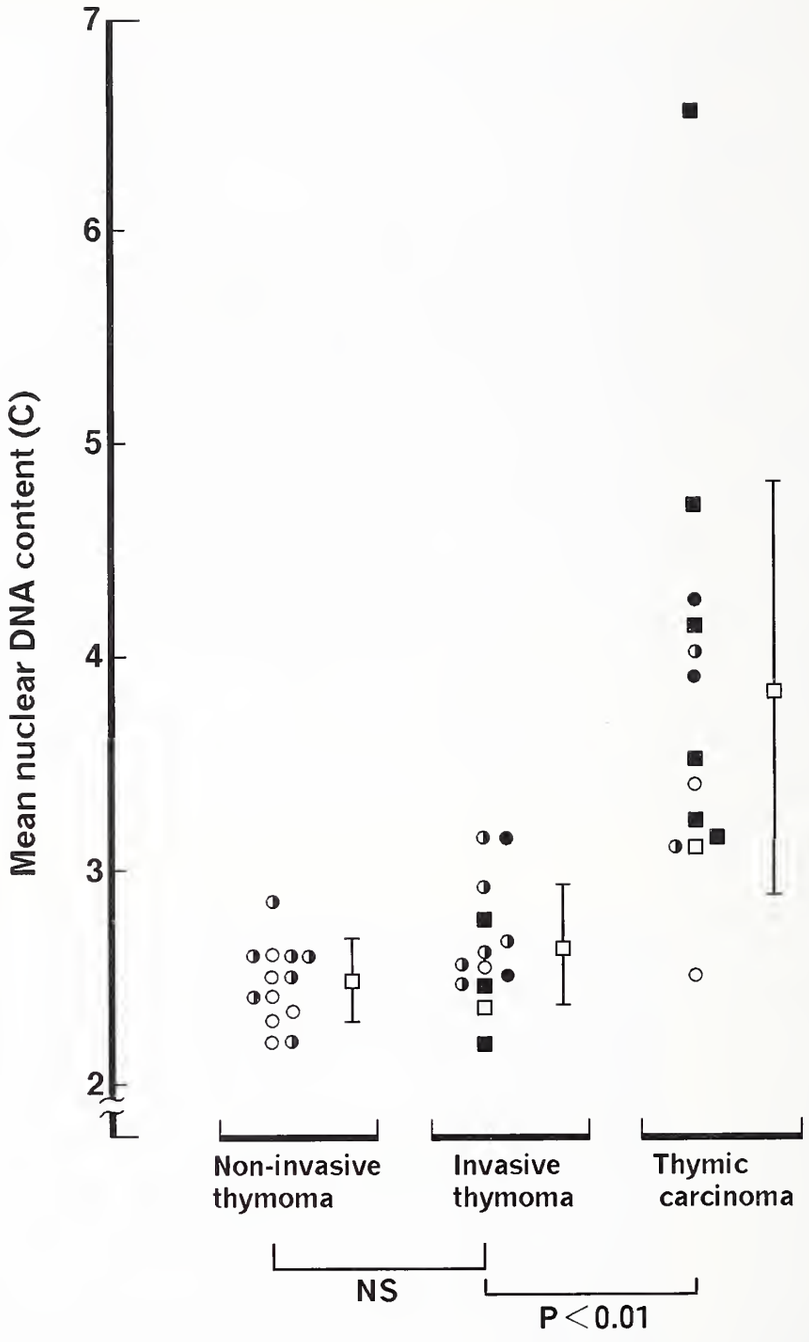


Figure 3-98
MEAN NUCLEAR DNA CONTENT OF NONINVASIVE THYMOMA, INVASIVE THYMOMA, AND THYMIC CARCINOMA

(Fig. 2 from Asamura H, Nakajima T, Mukai K, Noguchi M, Shimosato Y. Degree of malignancy of thymic epithelial tumors in terms of nuclear DNA content and nuclear area. Am J Pathol 1988; 133:615–22.)

were significantly higher than those of noninvasive and microinvasive thymomas, and that the proportion of aneuploidy as well as the S-phase fraction in grossly invasive thymomas were significantly higher than in noninvasive and microinvasive thymomas. According to Pich et al. (88a), the 10-year survival rate for patients with thymoma was 73 percent for diploid, but only 38 percent for aneuploid cases, a statistically significant difference. Although there is an opinion that flow cytometry is not a useful guide for predicting the malignant potential of thymic tumors or the prognosis of patients, the general consensus is that nuclear morphometry and nuclear DNA content analysis help in assessing the degree of malignancy and predicting the prognosis of patients with thymic epithelial tumors.

The relationship between the frequency of mitotic figures in epithelial cells and the degree of malignancy of the thymoma has not yet been studied in detail. Since the proliferative activity of tumor cells is considered to be one of several malignancy-associated factors in many tumors, such a study should be conducted for thymic epithelial tumors as well, not only by counting mitotic figures but also by examining proliferative

activity through immunostaining of proliferating cell nuclear antigen (PCNA) or proliferation-associated nuclear antigen (Ki-67), and probably by investigating genetic abnormalities in growth-related oncogenes and tumor suppressor genes. However, no clinically applicable results have been obtained by recent immunohistochemical cell kinetic studies of PCNA and Ki-67 in thymic epithelial tumors, although well-differentiated thymic carcinoma showed higher Ki-67 labeling indices compared with the medullary thymomas (by modified Müller-Hermelink and Kirchner classification [$p<0.05$]). Stage IV cases showed higher PCNA labeling indices than those of other stages ($p<0.05$). The results indicate that the differences in biologic behavior of the different histologic subtypes may be in part explained by differences in the tumor growth fraction (113a).

The argyrophilic proteins associated with the nuclear organizer regions (AgNORs) are related to cell proliferative activity. Pich et al. (88a) found that 10-year survival was 88 percent for patients with thymomas with 5.75 AgNORs per cell or fewer but only 34 percent for patients with thymomas with more than 5.75 AgNORs per cell (statistically significant), and that AgNOR counts as well as tumor stage retained independent prognostic significance on multivariate survival analysis.

Treatment and Prognosis. The primary treatment of thymoma is surgical removal (69); radiotherapy or chemotherapy is instituted in advanced cases, either alone or in combination with surgery. Thoracotomy is performed in most thymoma cases. Surgery includes simple resection of the part of the thymus containing the thymoma, total thymectomy, and combined resection of the tumor, both primary and implanted or metastatic tumors and adjacent organs such as the lung, mediastinal lymph nodes, a portion of the major vessels, pericardium, and diaphragm. In the large series of Lewis et al. (68), of 274 patients who underwent thoracotomy, 227 (83 percent) had total resection. Surgery may follow radiotherapy in some advanced cases. Postoperative radiotherapy is instituted after incomplete removal of the tumor, or even after complete removal of a tumor which is invasive or adherent to adjacent structures. Current recommendations for the management of thymoma by the Memorial Sloan-Kettering Cancer Center group are as follows (35a): 1) small tumors (less than 5 cm) that appear encapsulated should be resected and, if pathologically stage I, require no further treatment; 2) tumors greater than 5 cm or those that appear invasive by CT have a high local recurrence rate and a decreased patient survival and these patients should be considered for neoadjuvant therapy.

In the Lewis study (68), of 232 treated patients who were discharged with no evidence of disease, 125 (44 percent) were alive after follow-up periods ranging from 1 to 30 years; 38 (14 percent) died of thymoma; 46 (16 percent) died of myasthenia gravis; 63 (22 percent) died due to unrelated causes; and in 11 cases the cause of death was unknown. Recurrence occurred at or before 15 years of follow-up. Of 187 patients with circumscribed, noninvasive tumors who underwent complete resection, 22 (12 percent) had thoracic recurrences. Fechner (42), after a review of the literature, stated that less than 2 percent of benign encapsulated thymomas recurred after resection, and that recurrent tumors took one of two different forms, either pleural implants or localized mediastinal tumors.

Analyses of death rates reveal that poor prognostic factors significant to overall survival ($p<0.05$) are an age exceeding 60 years, presence of mediastinal or constitutional symptoms, invasive or metastasizing thymoma at diagnosis, tumor size greater than or equal to 15 cm, and a predominantly epithelial histologic subtype. Slightly higher death rates in patients with myasthenia gravis are of marginal statistic significance. Illustrative survival curves with respect to tumor death are shown in figure 3-93. The importance of histologic subclassification by cell type has been stressed by Quintanilla-Martinez et al. (fig. 3-94) (89).

Rarely, extrathoracic spread is seen. There were eight such cases in the series of Lewis et al. (38), involving the bone in five cases, extrathoracic lymph nodes in four, liver in three, and nervous system in two. Histologically, metastatic tumors maintain characteristic features of thymoma in many cases, but may show a decrease in the number of lymphocytes (figs. 3-58, 3-99).

Clinical Staging. Masaoka et al. (72) reported criteria for the clinical staging of thymic epithelial tumors (Table 3-6), and later proposed using the TNM classification (Table 3-7) (113). Although the former has been used by some investigators, we

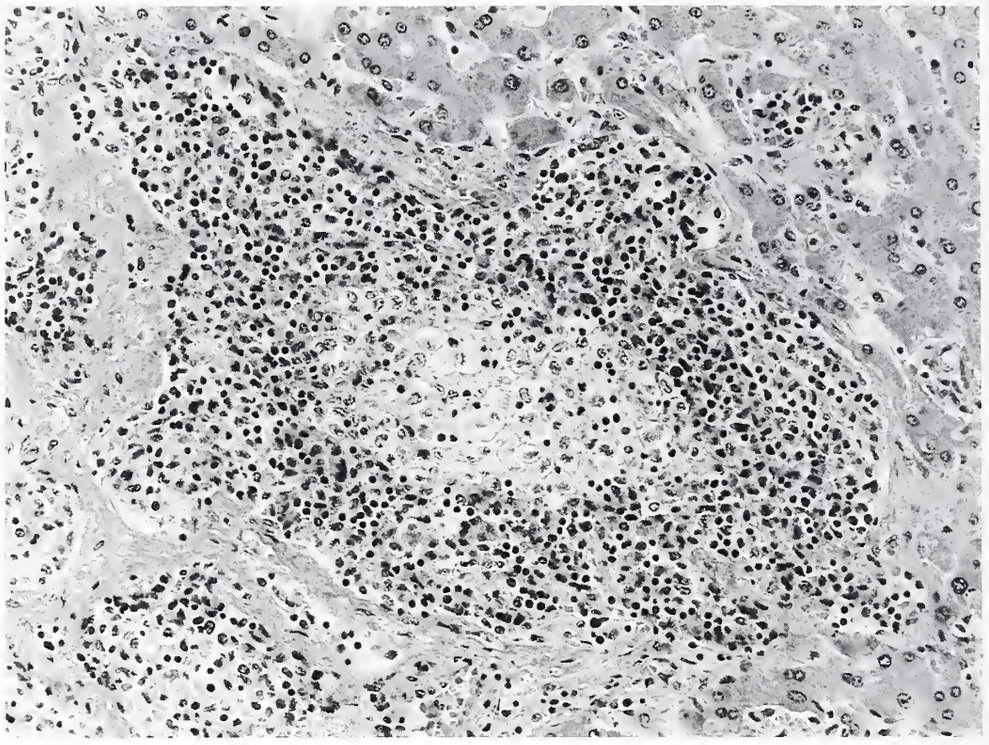


Figure 3-99
THYMOMA METASTATIC TO LIVER

Metastatic focus in liver shows aggregates of polygonal epithelial cells surrounded by a lymphocyte-rich zone (same case as that in figure 3-24).

Table 3-6

MASAOKA'S CLINICAL STAGE*

Stage I:	Macroscopically completely encapsulated and microscopically no capsular invasion
Stage II:	1. Macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or 2. Microscopic invasion into capsule
Stage III:	Macroscopic invasion into neighboring organs, i.e., pericardium, great vessels, or lung
Stage IVa:	Pleural or pericardial dissemination
Stage IVb:	Lymphogenous or hematogenous metastasis

*From reference 72.

Table 3-7

YAMAKAWA-MASAOKA TNM CLASSIFICATION AND STAGING*

T Factor

T1: Macroscopically completely encapsulated and microscopically no capsular invasion

T2: Macroscopically adhesion or invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule

T3: Invasion into neighboring organs, such as pericardium, great vessels, and lung

T4: Pleural or pericardial dissemination

N Factor

N0: No lymph node metastasis

N1: Metastasis to anterior mediastinal lymph nodes

N2: Metastasis to intrathoracic lymph nodes except anterior mediastinal lymph nodes

N3: Metastasis to extrathoracic lymph nodes

M Factor

M0: No hematogenous metastasis

M1: Hematogenous metastasis

Stage

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVa	T4	N0	M0
IVb	any T	N1, 2, or 3	M0
	any T	any N	M1

*From reference 113.

believe that a minor modification in wording should be made: that is, "invasion into the capsule" in stage II should be "transcapsular invasion" and "invasion into the pleura and pericardium" (stage III) should be defined more precisely, either as "adherent to but not penetrating through the pleura" (stage II) or "invading and exposed at the pleural (or pericardial) surface" (stage III) (Table 3-8). In our series, the number of cases in stage I according to Masaoka's criteria was only six; using our modification this

Table 3-8

PROPOSED PATHOLOGIC TUMOR EXTENT OF THYMIC EPITHELIAL TUMORS (National Cancer Center Hospital, Tokyo)*

pT1:	Completely encapsulated tumor
pT2:	Tumor breaking through capsule, invading thymus or fatty tissue (may be adherent to mediastinal pleura but not invading neighboring organs)
pT3:	Tumor breaking through the mediastinal pleura or pericardium, or invading neighboring organs such as great vessels and lung
pT4:	Tumor with pleural or pericardial implantation

*From reference 56.

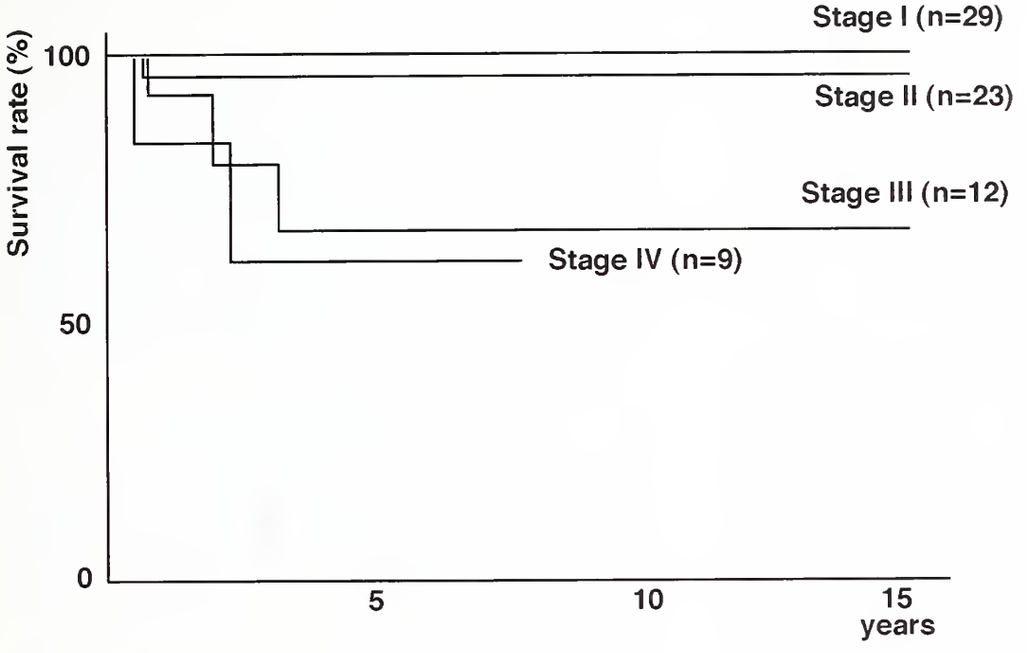


Figure 3-100
SURVIVAL CURVES OF PATIENTS WITH SURGICALLY RESECTED THYMOMA ACCORDING TO MODIFIED MASAOKA'S CLINICAL STAGE

(Fig. 10 from Koga K, Matsuno Y, Noguchi M, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and noninvasive thymoma. Pathol Int 1994;44:359–67.)

increases to 29, an adequate number for statistical analysis. However, by the use of either criteria, the survival curves for stages I and II are very close, as are those for stages III and IV, indicating that stages I and II, and stages III and IV could be combined (fig. 3-100). In other words, clinical staging may not be necessary for thymoma, which can be divided simply into noninvasive and invasive types because of the clear-cut difference in prognosis between the two groups (56), as also described by other investigators (34,68). Noninvasive thymoma here indicates circumscribed thymoma, which is confined to within the thymus or anterior mediastinum, whereas invasive thymoma is that involving neighboring organs or tissues such as the lung and pericardium. Using DNA flow cytometric analysis and clinical behavior, Kuo et al. (60) reported that microinvasive thymomas (grossly circumscribed invasive tumors, not involving the surrounding major structures or organs) do not have to be separated from noninvasive thymomas. However, Wilkins et al. (112) recommended postoperative radiotherapy for all patients in stages II and III, since 2 out of 23 patients with stage II disease died from thymoma between 5 and 10 years. The importance of microscopic assessment of invasion in stage II disease was emphasized by Quintanilla-Martinez et al. (89), when 1 of 16 stage IIa tumors recurred compared with 3 of 16 stage IIb tumors (89). Table 3-9 shows the number and causes of death in patients with surgically resected thymomas at our hospital according to modified Masaoka clinical stage (56). Most

Table 3-9

NUMBER AND CAUSE OF DEATH IN PATIENTS WITH SURGICALLY RESECTED THYMOMA BY MODIFIED MASAOKA'S CLINICAL STAGE

	Stage I	Stage II	Stage III	Stage IV
Total number of cases	29	23	12	9
Tumor death	0 (0.0)*	1 (4.3)	3 (25.0)	2 (22.2)
Death by other cause	2	3	0	3
	breast ca 1 liver cell ca 1	gastric ca 1 unknown 2		myasthenia gravis 2 pulmonary infarction 1

*Number in parentheses indicates percentage of tumor death in a given stage.

tumor deaths, five out of six, occurred in patients with advanced disease, stages III and IV. More detailed analysis of the fatal cases disclosed that one patient with a stage II predominantly lymphocytic and polygonal cell type thymoma was discharged from hospital after complete removal of the tumor, but died 5 months later at another hospital, where no autopsy was performed but the cause of death was reported to be the tumor. However, such rapid growth within 5 months is unbelievable for a circumscribed and completely removed thymoma. In one case of stage II predominantly lymphocytic and mixed cell type thymoma showing rosette-like structures (see fig. 3-60), the tumor showed vascular invasion histologically (fig. 3-95), and recurred after complete removal, but the patient was still alive with tumor 11 years after surgery for the primary tumor.

Tumor deaths among our cases were observed within 3 years after the first surgery, regardless of complete or incomplete removal of the tumor. If the tumor recurred more than 3 years after the first surgery, the prognosis was relatively good despite recurrence, indicating a slow growth of the thymoma in cases showing late recurrence. It can be extrapolated from these observations that the pathologic stage at the time of initial surgery may be regarded as a parameter of tumor aggressiveness, which influences the outcome of the disease; that is, tumors at stages I and II frequently show slow growth in comparison with those at stages III and IV, which often proliferate rapidly. Therefore, we believe that the prognosis of patients with thymoma should be predicted on the basis of both disease stage and tumor aggressiveness. Assessment of tumor aggressiveness can be done by cell typing as proposed by Marino and Müller-Hermelink, and Kirchner et al. (53,70) or by cell typing and degree of cell atypia as proposed by Lewis et al. (68). However, more accurate and objective methods for assessing the aggressiveness of tumors should be explored.

Thymic Carcinoma

Definition. In the previous Fascicle on thymic tumors, thymic carcinoma was included in the category of "thymoma" (141). Malignant thymoma included tumors with features characteristic of thymoma (either predominantly epithelial, predominantly lymphocytic, or mixed epithelial and lymphocytic) with local invasion including pleural implantation or with true lymphatic or hematogenous metastasis, and tumors with features characteristic of carcinoma as seen in other organs, with or without evidence of metastasis; these tumor types were designated later as malignant thymoma of types I and II, respectively (128). Such a classification is understandable and still accepted by some investigators because the term "thymoma" in a wide sense includes every thymic epithelial tumor irrespective of histology, and because distinction of "benign" encapsulated thymoma from type I malignant thymoma is often impossible by histology alone and type II malignant thymoma is a rare tumor. In the same paper, Levine and Rosai used the terms "encapsulated thymoma," "truly invasive thymoma," and "thymic

carcinoma." We support this subtyping, but view thymic epithelial tumors differently. First, the suffix "-oma" means tumor or neoplasm, usually denoting those of a benign nature in most organs or tissues, and rarely malignant tumors such as seminoma and hepatoma. Second, we are now in a position to be able to categorize tumors clearly as benign, or of intermediate, low-grade, or high-grade malignancy. Third, it is possible to separate tumors into different entities clearly, not only on the basis of morphology, but also by their functions. From our standpoint, thymoma, as already stated, is defined as a cytologically bland epithelial tumor of the thymus with various amounts of associated immature T cells, which may be locally invasive but rarely metastasizes via lymphatics or blood vessels. That is, thymoma is a potentially malignant or low-grade malignant tumor with mild nuclear atypia and low proliferative activity, whose invasiveness and metastatic potential cannot be predicted from histology alone, except for spindle cell type thymoma, most of which are benign. The incidence of extrathoracic metastasis was about 10 in 200 thymomas at the Mayo Clinic (155). On the other hand, thymic carcinoma is defined as a thymic epithelial tumor with a high degree of histologic anaplasia, obvious cell atypia, and increased proliferative activity, which closely resembles carcinomas seen in other organs (146, 147,150,151,155) and is unassociated with immature T cells (143).

Synonyms and related terms include *invasive thymoma, type II malignant thymoma, metastasizing thymoma,* and a variety of subtypes such as squamous cell carcinoma, epidermoid carcinoma, adenosquamous carcinoma, mucoepidermoid carcinoma, basaloid carcinoma, lymphoepithelioma, lymphoepithelioma-like carcinoma, small cell carcinoma, neuroendocrine carcinoma, undifferentiated carcinoma, anaplastic carcinoma, clear cell carcinoma, and sarcomatoid carcinoma.

Müller-Hermelink and coworkers, who divided thymoma into cortical, medullary, and mixed types based on the microscopic features of the epithelial cells, also followed the classification of Levine and Rosai in their earlier publications in 1985, and the term thymus carcinoma was used for all tumors characterized by invasive growth of almost pure epithelial cells, which corresponds to type II malignant thymoma (128,130,138). Recently, however, they proposed an entity of well-differentiated thymic carcinoma of low-grade malignancy, previously classified as cortical thymoma (121,122). We consider this to be invasive thymoma (or type I malignant thymoma) with some increase in anaplasia and proliferative activity of individual cells, a tendency to be predominantly epithelial or partly "epidermoid," and with a significantly increased risk of relapse and death as compared with other histologic types of thymoma (140). Our opinion that well-differentiated thymic carcinoma as defined by Müller-Hermelink et al. is a form of invasive thymoma is supported by the frequent association of myasthenia gravis and the presence of immature T cells in some tumors, neither of which has been seen in the thymic carcinomas we have analyzed.

In this chapter we deal with thymic carcinoma by our definition, that is, malignant thymoma of type II by the Levine and Rosai classification (128), and several subtypes of thymic carcinoma exclusive of low-grade well-differentiated thymic carcinoma of Kirchner et al. (122).

General and Clinical Features. Because of the relative rarity of thymic carcinoma, the wide variation of its histology, and the differences in diagnostic criteria among investigators, its exact incidence in any given country and geographic differences in frequency are unknown. The largest series, that of Suster and Rosai (147), is made up of consultation cases. The largest series from a single institution, reported by Wick et al. (155), comprises 20 cases collected over 75 years at the Mayo Clinic, during which more than 200 thymomas were assessed. The 13 cases reported by Truong et al. (150) were collected from two hospitals over a 22-year period. In all, 62 cases are reported in the literature. Our cases, obtained in a cancer hospital, comprise 17 surgically resected thymic carcinomas and an additional 5 biopsy cases of probable thymic carcinoma covering a 29-year period during which 79 thymomas and about 2,500 lung cancers were resected. From an analysis of subtypes in the literature, there appears to be a difference in geographic incidence: a higher frequency of well-differentiated squamous cell carcinoma and a much lower frequency of small cell carcinoma in the Orient than in the United States (126,145,147,150,155).

Most cases reported from various institutions occurred in cancer-age patients; only a few patients were below the age of 30 years, and the

youngest was a 4-year-old. However, 25 of the 60 consultation cases of Suster and Rosai (147) occurred in patients under 40 years of age. This inconsistency cannot be explained at present. The male to female ratio also varies from almost equal to 2.3 to 1, contrasting with a tendency toward female predominance among patients with thymoma.

Multiplicity has rarely been reported (137), although this has to be verified by excluding the possibility of intrathymic metastasis. Etiologic factors have not been clarified. A possible association of Epstein-Barr virus with undifferentiated (lymphoepithelioma-like) carcinoma is discussed separately.

The most frequent symptoms are chest pain or dull ache. Coughing and general symptoms such as fatigue, fever, anorexia, and weight loss may also be present. Superior vena cava syndrome may be observed. In asymptomatic patients, tumors are sometimes found by routine chest X-ray examination. There have been no reports of accompanying paraneoplastic syndromes such as myasthenia gravis or pure red cell aplasia, although a few thymomas associated with myasthenia gravis have progressed to thymic carcinoma (147), and frequent association of myasthenia gravis was reported in "well-differentiated thymic carcinoma" (122); we consider the latter invasive thymoma and discuss it in the chapter on thymoma.

A tumor in the anterior mediastinum can be detected by imaging techniques in almost every instance, either by chest X ray or computed tomography (CT) (fig. 3-101). Cystic changes and calcium deposits are rare. Frequently, the abnormal density involves the neighboring organs, such as the lungs, pericardium, and major vessels. However, transbronchial biopsy or cytology with the aid of a fiberoptic bronchoscope fails to reveal a tumor in most cases.

Imaging techniques are of no value for determination of tumor type, and the diagnosis is made by either percutaneous needle biopsy with a Sure-cut or Tru-cut needle (fig. 3-102), or aspiration cytology or biopsy at the time of mediastinoscopy. Biopsy may yield only or predominantly necrotic or crushed tissue (fig. 3-103), and it should be repeated if necessary. Thymic carcinoma should be distinguished from predominantly epithelial thymoma, malignant germ cell tumors such as embryonal carcinoma, or diffuse large cell lymphoma with sclerosis. It may be difficult to determine whether the carcinoma is primary in the mediastinum or metastatic, unless clinical findings suggest a primary mediastinal tumor and biopsy specimens show features characteristic of thymic carcinoma.

The treatment of choice depends upon the stage of the disease and the tumor histology. The relevance of TNM classification and staging is being discussed at present. Masaoka's clinical staging for thymoma (Table 3-6) (131) is not applicable to thymic carcinoma, although a fairly good correlation with survival and staging was noted in Suster's cases (147). The TNM classification recently reported by Masaoka et al. (156), and a staging system used tentatively in our institute (151) are shown in Tables 3-7 and 3-10, and should be evaluated by others.

For treatment purposes, Suster and Rosai (147) divided thymic carcinomas into two groups: those with low-grade and those with high-grade histology. For tumors with low-grade histology, resection followed by radiotherapy is reported to be sufficient in most resectable cases, and we feel that if the tumor is localized within the thymus and completely resected, postoperative radiotherapy may not be necessary. On the other hand, most advanced low-grade and high-grade tumors have an unfavorable outcome even with a combination of surgery, radiation, and chemotherapy. High-grade tumors must be detected while still confined within the anterior mediastinum without metastases. Treatment results in our cases were similar to those reported by Suster and Rosai, except for some cases of squamous cell carcinoma with unfavorable outcome.

The most frequent sites of metastases are lymph nodes (mediastinal, cervical, and axillary), followed by bone, lung, liver, and brain. Lymphatic spread within the thymus is seen occasionally (fig. 3-104), confirming the necessity for complete removal of the thymus in cases of thymic carcinoma and also thymoma. Factors associated with the prognosis of patients are histology, status of the primary tumor (circumscription), lobulation, and mitotic activity (147).

Gross Findings. The gross features of thymic carcinoma vary depending on tumor histology and size. In our cases, tumor diameter ranged from 3 to 5 cm or more. Squamous cell carcinoma

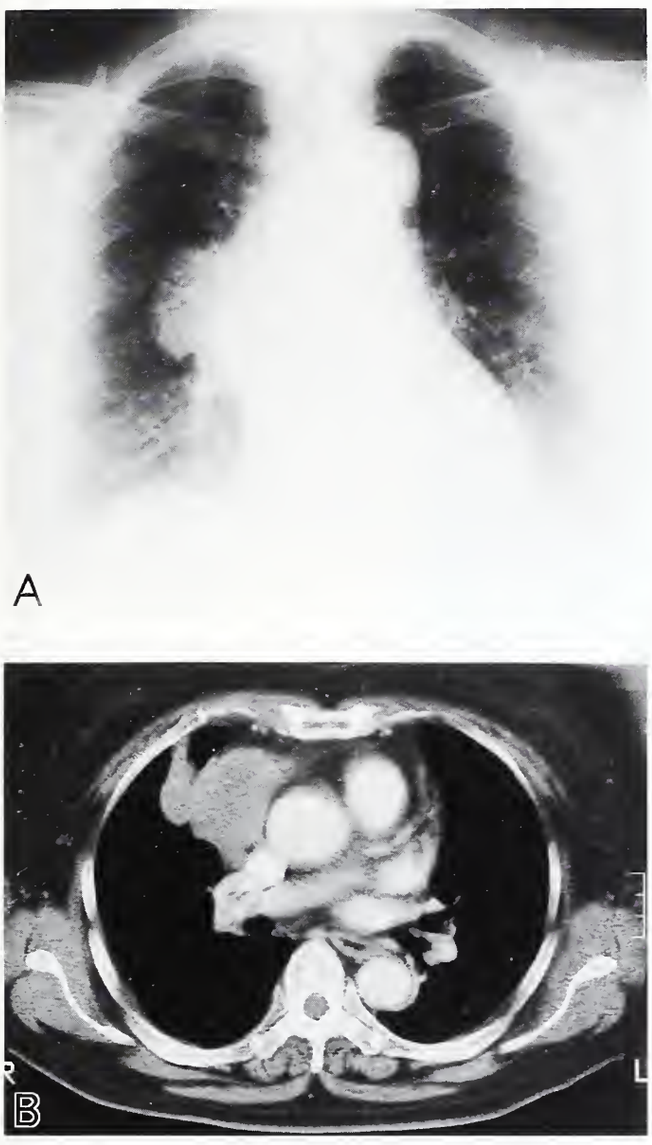


Figure 3-101
THYMIC CARCINOMA

A: Posterior-anterior chest roentgenogram reveals an irregular but well-defined density with a base located in the mediastinum, projecting into the right mid-lung field. Pulmonary vasculature shows no abnormality. The nodular density overlapping the density of the superior vena cava is considered to be enlarged mediastinal lymph nodes, which obscure the paratracheal stripe. An oblique view disclosed that the abnormal density was located in the anterior mediastinum.

B: Computed tomography discloses an irregular but homogeneous density in the anterior mediastinum, which faces the density of the ascending aorta and invades S3 (anterior segment) of the right upper lobe of the lung.

C: Horizontal section of the tumor reveals that the main tumor in the anterior mediastinum has irregular invasive borders and a fibrotic central portion with small scattered foci of coagulation necrosis. Three nodules with scanty anthracotic pigments on the left side of the tumor represent tumor invasion into the lung. The border of the tumor on the right of the photograph shows pseudoencapsulation, which abuts on the ascending aorta. Thymic tissue is attached anterior to the tumor.

with keratinization (low-grade histology by the Suster and Rosai scheme) is firm, with a rather homogeneous, ivory-colored cut surface and a scalloped border. Granularity may be noted, but lobulation is not evident or is inconspicuous, and the central parts are often sclerotic; infrequently, there are small foci of necrosis and cystic changes (figs. 3-105, 3-106). A false capsule is seen where the tumor reaches the capsule of the thymus, pleura, and pericardium. A true capsule is rare unless it develops from thymoma (fig. 3-107). A partially encapsulated basaloid carcinoma is shown in fig. 3-108.

The degree of coagulation necrosis and the areas of hemorrhage tend to increase in less differentiated tumors, or in tumors of high-grade

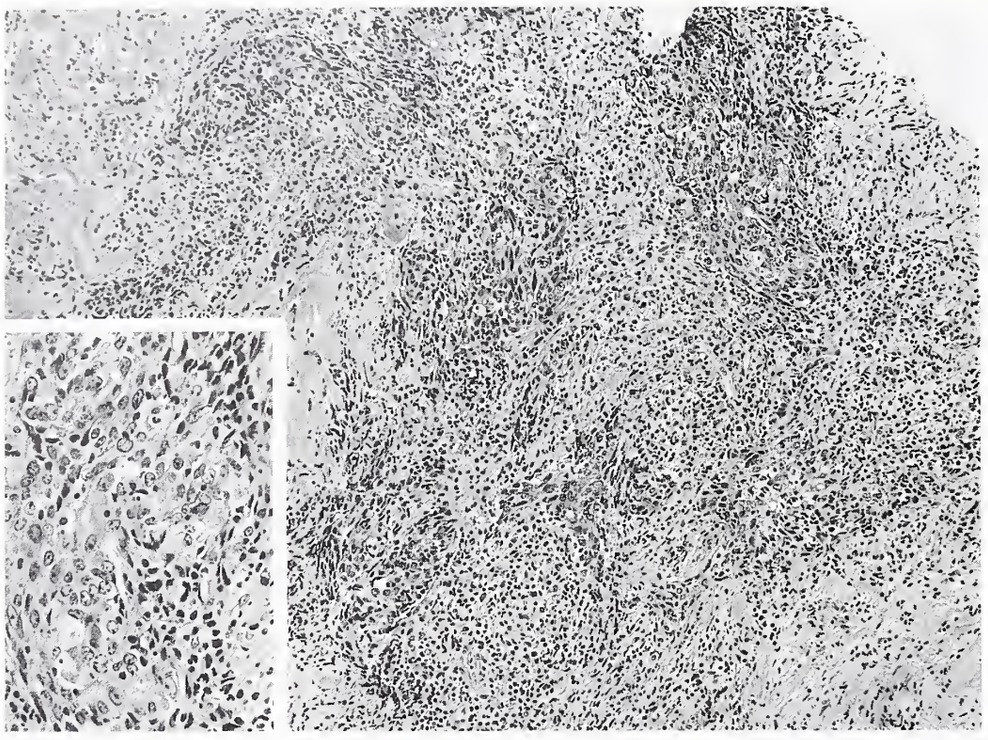


Figure 3-102
THYMIC CARCINOMA DIAGNOSED BY PERCUTANEOUS NEEDLE BIOPSY

Irregular solid nests of infiltrating tumor are composed of polygonal to short spindle cells with hyperchromatic nuclei and distinct nucleoli. A partially sclerotic fibrous stroma is partly infiltrated by lymphocytes and plasma cells. Inset: Higher power view of a poorly differentiated carcinoma nest.

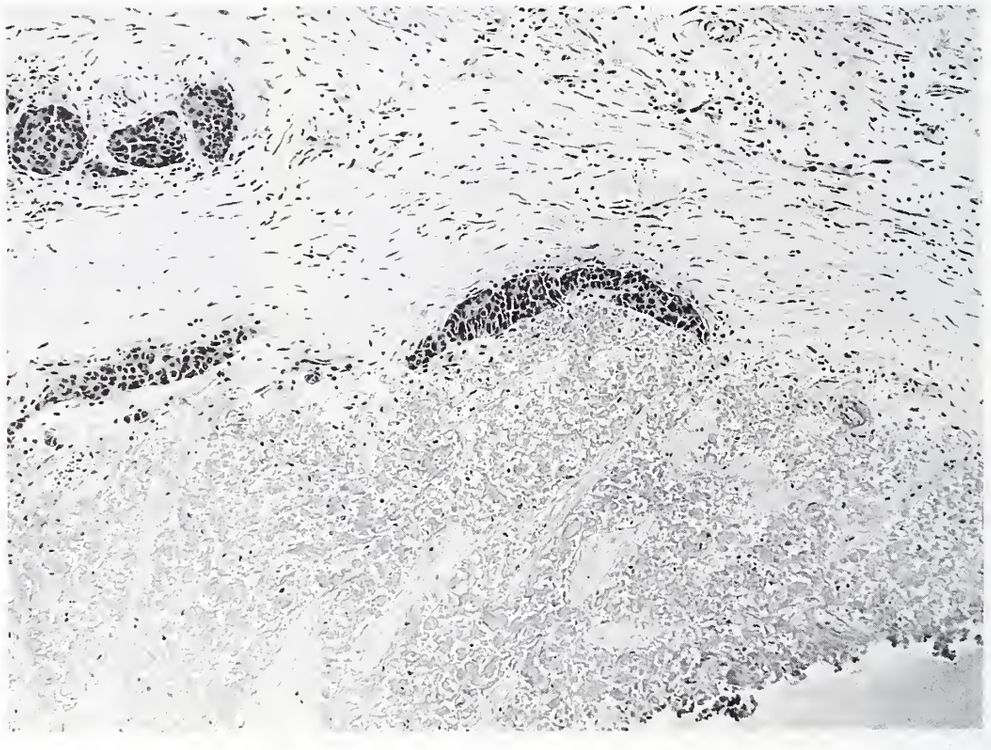


Figure 3-103
THYMIC CARCINOMA DIAGNOSED BY PERCUTANEOUS NEEDLE BIOPSY

An extensively necrotic tumor is bordered by fibrous tissue. Scanty, apparently viable tumor cell nests at the periphery of the tumor suggest a squamous cell nature.

histology. In some undifferentiated tumors, the surgical specimens consist of blood-stained fragments, probably because en bloc resection is impossible.

Microscopic Findings and Histologic Subtypes. Microscopically, thymic carcinoma constitutes a heterogeneous group of tumors. The histologic subtypings employed by several investigators are listed in Table 3-11 (147,150,151,155). In the United States, the most common type is lymphoepithelioma-like carcinoma (poorly differentiated squamous cell carcinoma) followed by small cell/neuroendocrine carcinoma. However, in our institute, squamous cell carcinoma is by far the most common, followed by undifferentiated large

Table 3-10

PROPOSED PATHOLOGICAL TNM AND STAGING OF THYMIC EPITHELIAL TUMOR (National Cancer Center Hospital, Tokyo)*

pT

pT1: Completely encapsulated tumor

pT2: Tumor breaking through capsule, invading thymus or fatty tissue (may be adherent to mediastinal pleura but not invading neighboring organs)

pT3: Tumor breaking through the mediastinal pleura or pericardium, or invading neighboring organs, such as great vessels and lung

pT4: Tumor with pleural or pericardial implantation

pN

pN0: No lymph node metastasis

pN1: Metastasis in anterior mediastinal lymph nodes

pN2: Metastasis in intrathoracic lymph nodes excluding anterior mediastinal lymph nodes

pN3: Metastasis in extrathoracic lymph nodes

pM

M0: No distant organ metastasis

M1: With distant organ metastasis

Pathologic stage grouping

Stage I	T1, T2	N0	M0
Stage II	T1, T2	N1	M0
Stage III	T3	N0, N1	M0
Stage IVa	T4	N0, N1	M0
IVb	any T	N2, N3	M0
IVc	any T	any N	M1

*From reference 151.

Figure 3-104
LYMPHATIC EXTENSION OF THYMIC CARCINOMA WITHIN THYMIC TISSUE

Small, irregularly shaped, solid tumor nests are present within the thymic tissue, which is in the vicinity of a main tumor. Germinal centers and a calcified Hassall corpuscle are also evident.

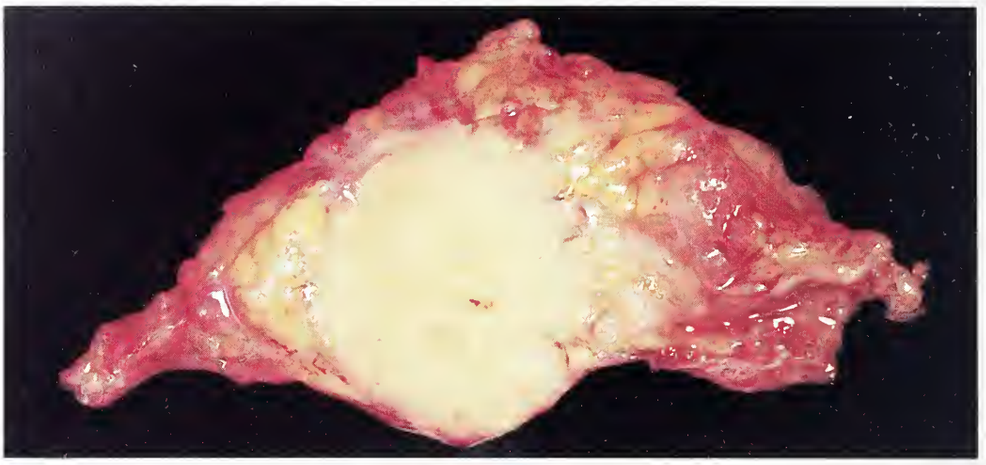


Figure 3-105
WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA

A tumor about 3 cm in diameter is present within the thymus. It is ivory-colored and homogeneous, with a sclerotic center and scalloped borders. No lobulation is noted.

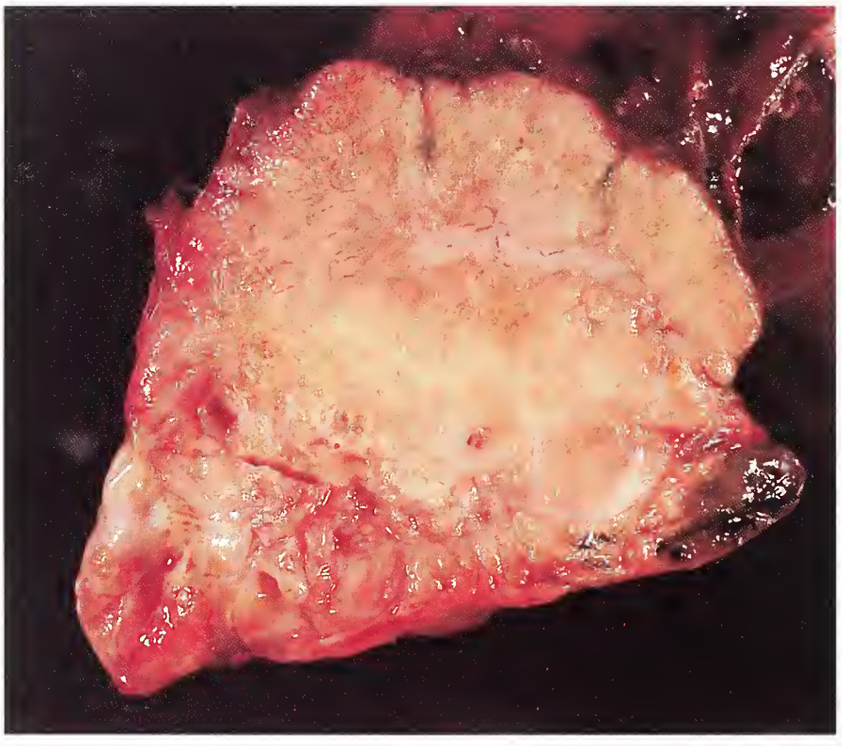


Figure 3-106
WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA INVADING THE LUNG

The tumor is centrally sclerotic and granular in the peripheral portion. The granularity is reflected by solid tumor nests bordered by bands of fibrous connective tissue. Because of compressive growth, no anthracotic pigments are present within the tumor. The lung tissue is evident in the right upper corner, and swollen lymph nodes are located in the right lower corner of the photograph.

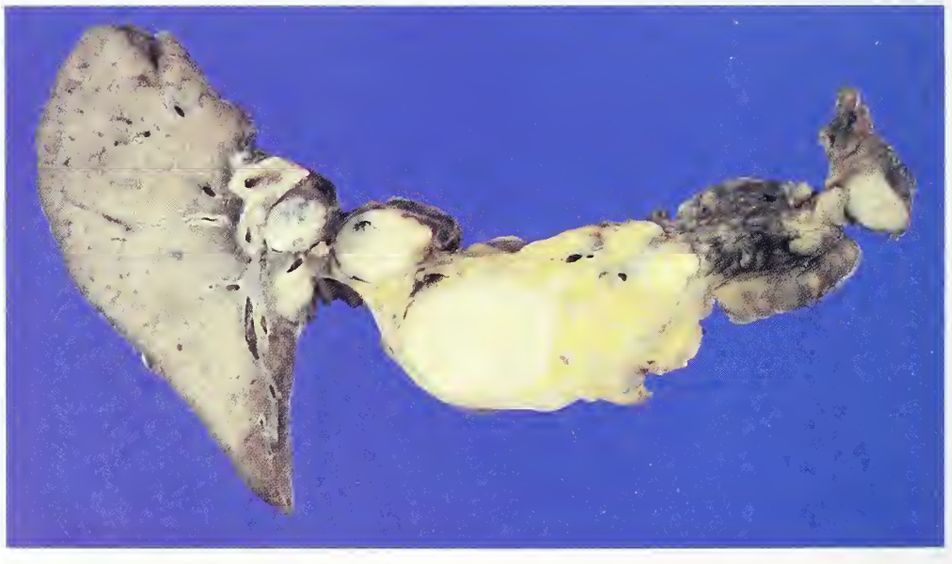


Figure 3-107
HORIZONTAL SECTION OF THE THYMUS WITH MULTIPLE TUMORS

Multiple tumors range from minute to 3.3 cm in diameter. The larger tumors are encapsulated at least partially, and contain squamous cell carcinoma. This is a case of squamous cell carcinoma that appears to have progressed from thymoma. (Fig. 3 from Morinaga S, Sato Y, Shimosato Y, Sinkai T, Tsuchiya R. Multiple thymic squamous cell carcinomas associated with mixed type thymoma. Am J Surg Pathol 1987;11:982–8.)

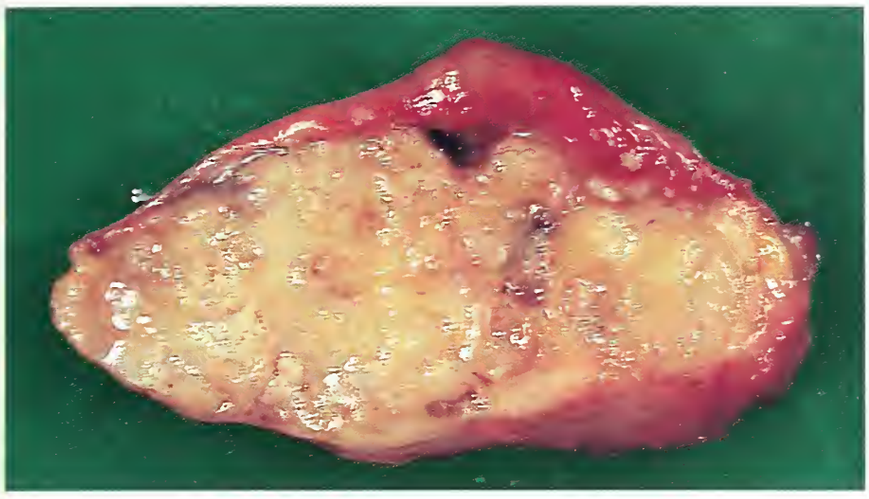


Figure 3-108
BASALOID CARCINOMA
The tumor is confined to within the thymic tissue and associated with a few cystic spaces. It is partly encapsulated and partly invasive.

Table 3-11

HISTOLOGIC SUBTYPING OF THYMIC CARCINOMA

Wick et al. (1982)	Truong et al. (1990)	Suster & Rosai (1991)	Shimosato et al.
		Low-grade histology	
Squamous cell carcinoma	Squamous cell carcinoma	Well-differentiated (keratinizing) squamous cell carcinoma	Squamous cell carcinoma well, moderately, and poorly differentiated
Spindle cell squamous carcinoma			
		Basaloid carcinoma	Mucoepidermoid carcinoma Adenosquamous carcinoma
	Adenosquamous carcinoma	Well-differentiated mucoepidermoid carinoma	Basaloid carcinoma
Lymphoepithelioma-like poorly differentiated squamous cell carcinoma		High-grade histology	Adenocarcinoma
		Lymphoepithelioma-like carcinoma	Lymphoepithelioma-like carcinoma
Small cell neuroendocrine carcinoma	Small cell carcinoma	Small cell neuroendocrine carcinoma	Small cell carcinoma
		Undifferentiated/anaplastic carcinoma	Large cell carcinoma (clear cell carcinoma)
	Clear cell carcinoma	Clear cell carcinoma	
Sarcomatoid carcinoma		Sarcomatoid carcinoma	Sarcomatoid carcinoma

cell carcinoma. Lymphoepithelioma-like carcinoma is infrequent, and no cases of small cell/neuroendocrine carcinoma, mucoepidermoid carcinoma, or clear cell carcinoma have been seen. This may represent a racial difference in the histology of thymic carcinoma.

Squamous Cell Carcinoma. Differentiated squamous cell carcinoma of low-grade histology (145,147) is characterized by solid nests of polygonal cells, often with vesicular nuclei, moderately prominent round nucleoli, a small to moderate amount of eosinophilic cytoplasm, and

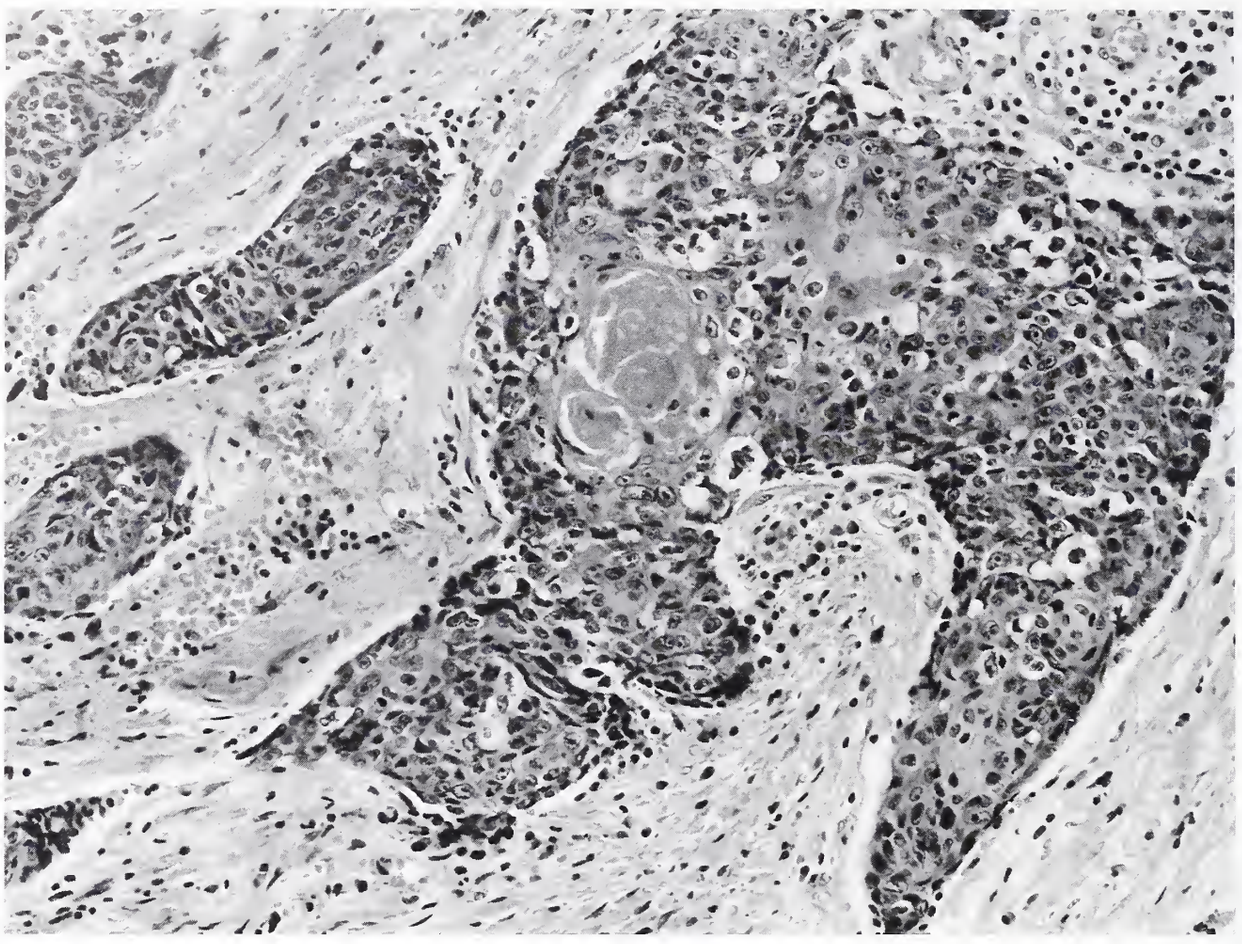


Figure 3-109
WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA
Solid geographical nests are made up of polygonal cells with oval nuclei and moderately prominent nucleoli showing keratinization. They are separated characteristically by broad bands of fibrous tissue.

well-defined cell borders showing keratinization and intercellular bridges in some areas (fig. 3-109). Keratinization may be abrupt, resembling Hassall corpuscles. Palisading or a radial arrangement of cells at the borders of nests, as often seen in squamous cell carcinoma of the lung and esophagus, is not commonly observed (figs. 3-109, 3-110). Tumor cell nests are surrounded by a broad zone of fibrous stroma, which is often hyalinized in the central portion of the tumor (fig. 3-111). Coagulation necrosis in the central portion of tumor nests is either absent or minimal and rarely seen in tumors of differentiated form or low-grade histology. Tumor cell nests in some areas have a lobular arrangement, with intermingled epithelial cells and lymphocytes, and closely associated fine blood vessels, simulating mixed epithelial and lymphocytic thymoma (fig. 3-112). However, the phenotypes of the lymphocytes here do not resemble those seen in thymoma but rather those encountered in cancers of other organs: CD1a-, CD3+, and CD4 or CD8+ (fig. 3-113). Plasma cells and eosinophils may also be found. The number of mitotic figures varies from area to area and from case to case.

In less differentiated squamous cell carcinoma, keratotic foci are rare but intercellular bridges can be identified in some areas. However, the general arrangement of the tumor cells is similar to that of the differentiated form (145,147). The amount of coagulation necrosis increases in the less differentiated form (fig. 3-114). Typical perivascular spaces seen in thymoma are rarely present in thymic carcinoma, but we have observed probable organizing perivascular spaces in poorly differentiated squamous cell carcinoma (fig. 3-115).

A case of well-differentiated papillary squamous cell carcinoma arising in a preexisting

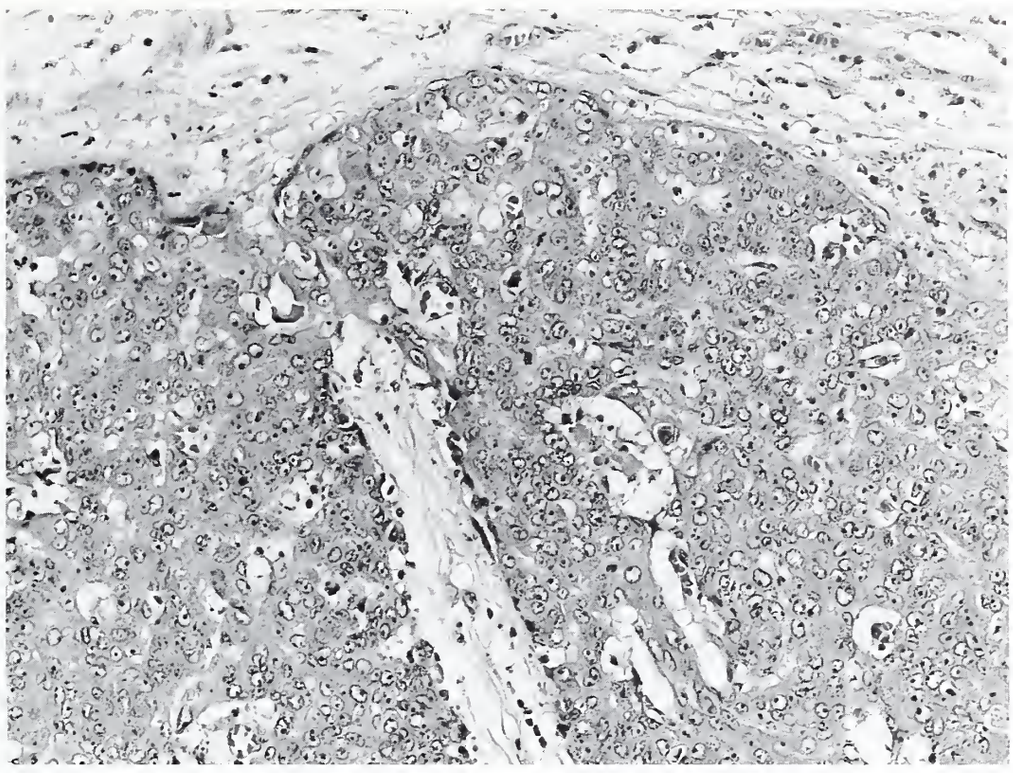


Figure 3-110
WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA

Solid tumor nests in this area are composed of polygonal cells with vesicular nuclei, prominent nucleoli, and keratotic tendency. Note that palisading of tumor cells at the border of nests is not evident.

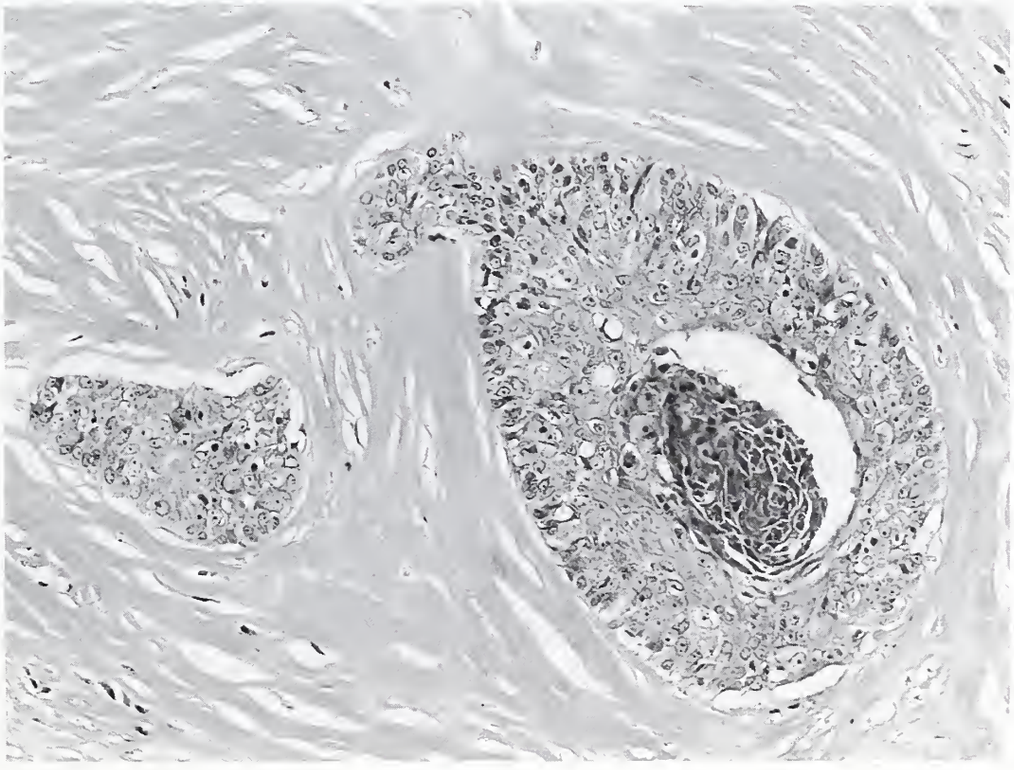


Figure 3-111
WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA

Nests of squamous cell carcinoma showing keratinization are bordered by broad bands of hyalinized stroma. Note the prominent round nucleoli in the vesicular nuclei of cancer cells.

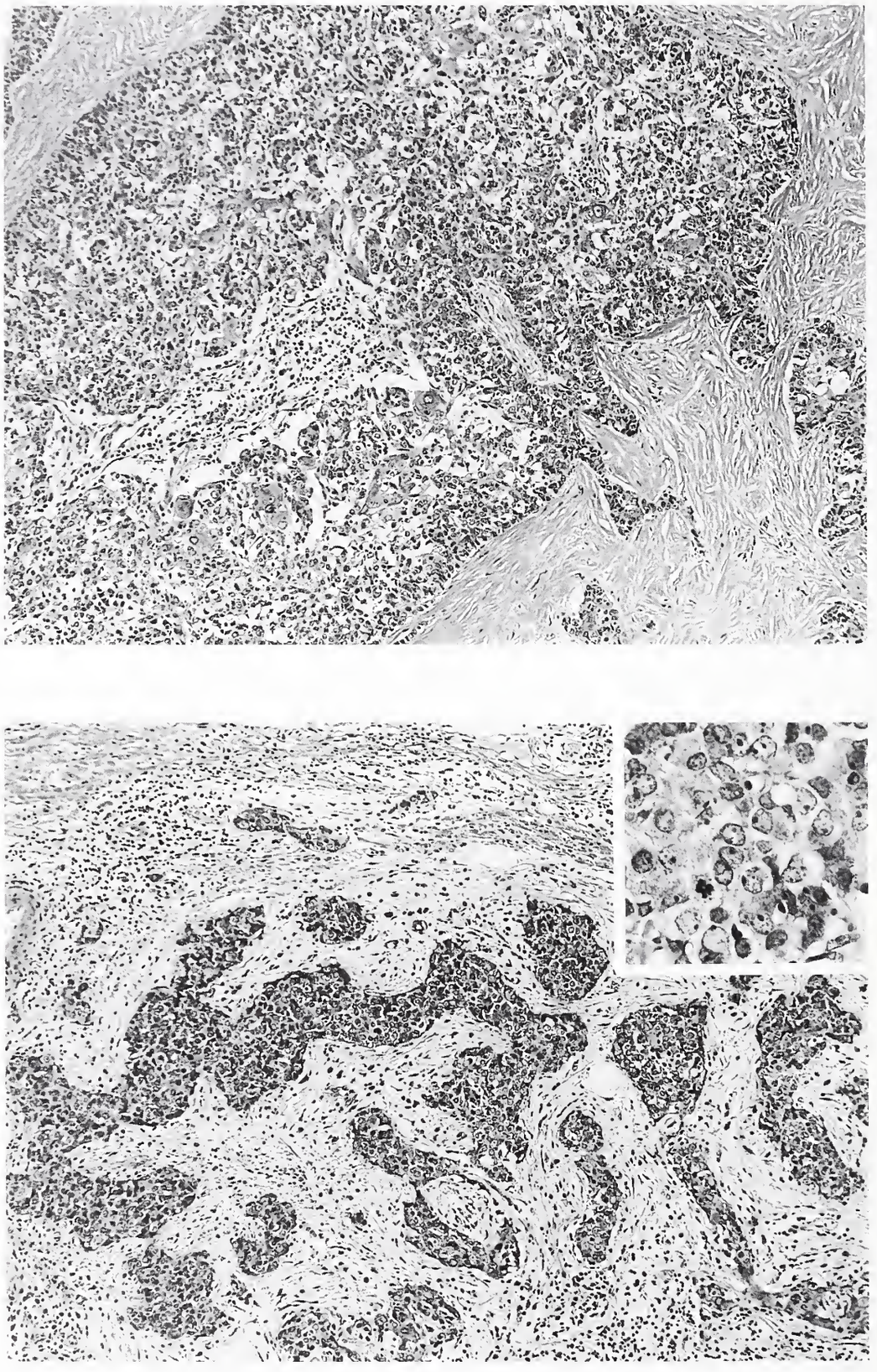


Figure 3-112

WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA PARTLY SIMULATING THYMOMA

Top: Solid nests near the central portion of the tumor show foci of keratinization and are infiltrated by lymphocytes, reminiscent of thymoma. The stroma within the nest is loose, suggestive of an organized perivascular space, but that surrounding it is sclerotic.

Bottom: Near the periphery and advancing borders of the tumor, nests are composed of less differentiated and more atypical cells with coarsely granular nuclei and prominent nucleoli. The loosely arranged stroma is infiltrated by lymphocytes. This feature is not one of thymoma but of carcinoma. Inset: Higher power view.

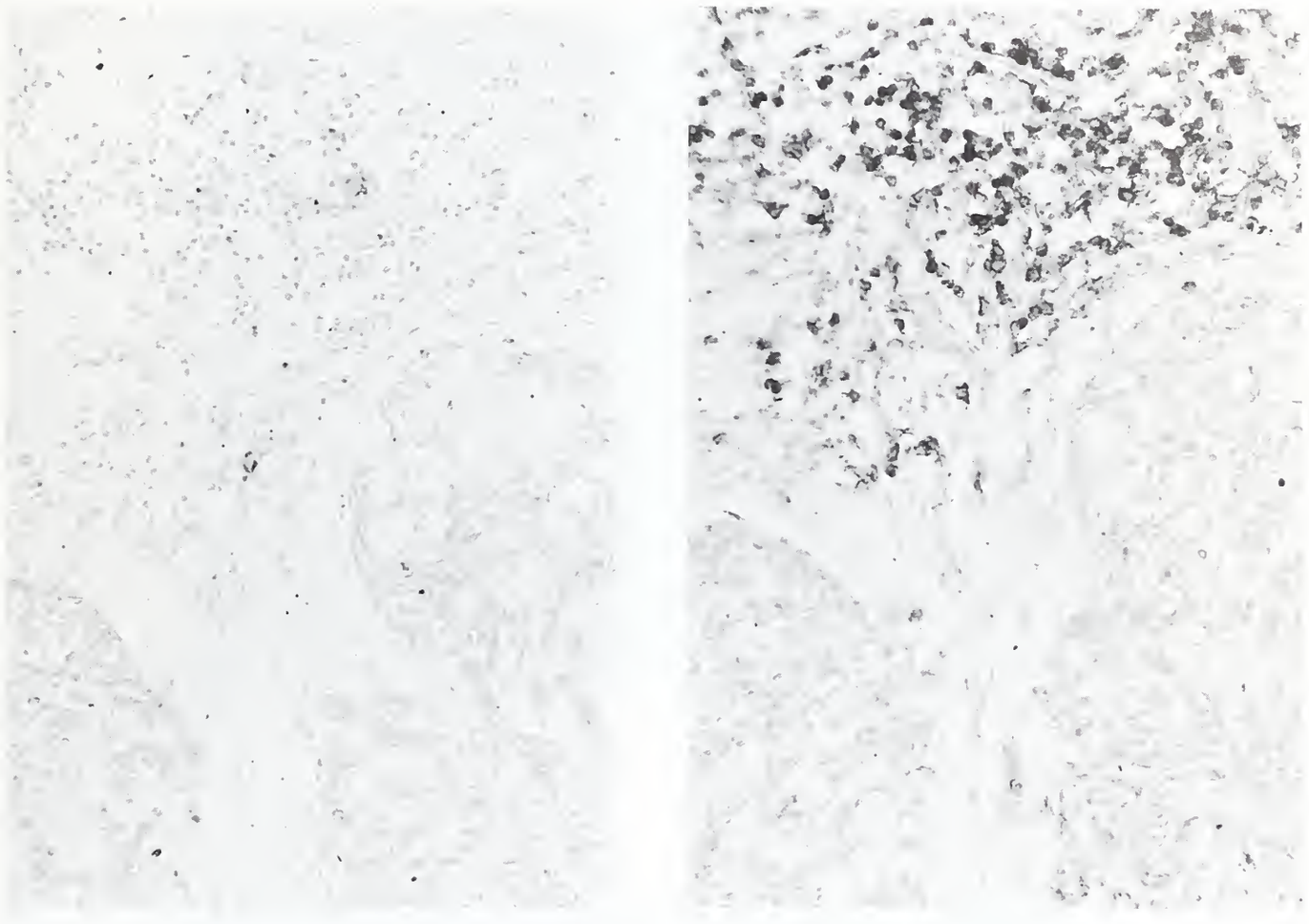


Figure 3-113
IMMUNOSTAINING FOR LYMPHOCYTE SURFACE MARKERS
IN SQUAMOUS CELL CARCINOMA (FROZEN SECTIONS)

Left: CD1a-positive lymphocytes are hardly evident.

Right: More than half of the lymphocytes in the stroma are CD4 positive (remaining cells are CD8 positive). This indicates that the majority of infiltrating lymphocytes are mature T cells, as is the case in cancers of other organs.

thymic cyst was reported (127). Squamous cell carcinoma coexisting with thymoma is uncommon (137): Truong et al. reported two cases (150), and Kuo et al. (126) found a spindle cell thymoma and lymphoepithelioma-like carcinoma together; the latter may be considered a variety of poorly differentiated squamous cell carcinoma. They also saw a cystic thymoma and coexistent keratinizing squamous cell carcinoma. Wick et al. (155) described a thymoma together with lymphoepithelioma-like carcinoma. Suster and Moran (146a) studied 22 thymic epithelial tumors characterized by the admixture of areas displaying features of thymoma and areas showing features of thymic carcinoma. Histologically, a combination of thymoma and well-differentiated squamous cell carcinoma was seen in 10 cases, thymoma and poorly differentiated squamous cell carcinoma in 7, and spindle cell thymoma with poorly differentiated squamous cell carcinoma in 5. Features of clear cell carcinoma or lymphoepithelioma-like carcinoma were seen in some cases.

One of two cases we studied revealed multiple tumors in the thymus, some of which were mixed epithelial and lymphocytic thymoma, while others showed features of carcinoma consisting of keratinizing squamous cell carcinoma in some areas and poorly differentiated large cell carcinoma in others. Transition from thymoma to carcinoma was also observed (figs. 3-107, 3-116). Our other case was a 36-year-old male, in whom myasthenia gravis was diagnosed at the age of 21, thymectomy was carried out at the age of 23, a locally recurrent tumor was removed and followed

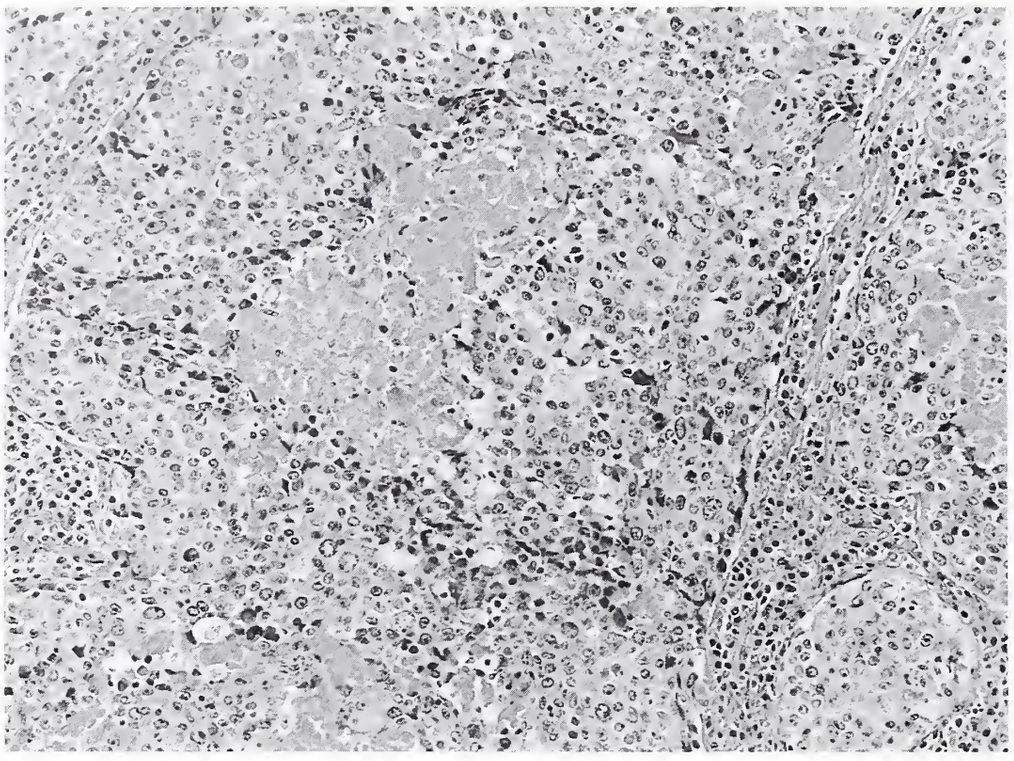


Figure 3-114
POORLY DIFFERENTIATED CARCINOMA METASTASIS IN A CERVICAL LYMPH NODE
Large solid nests showing central coagulation necrosis consist of polygonal cells with vesicular nuclei and moderately prominent nucleoli (same case as that in figure 3-109).

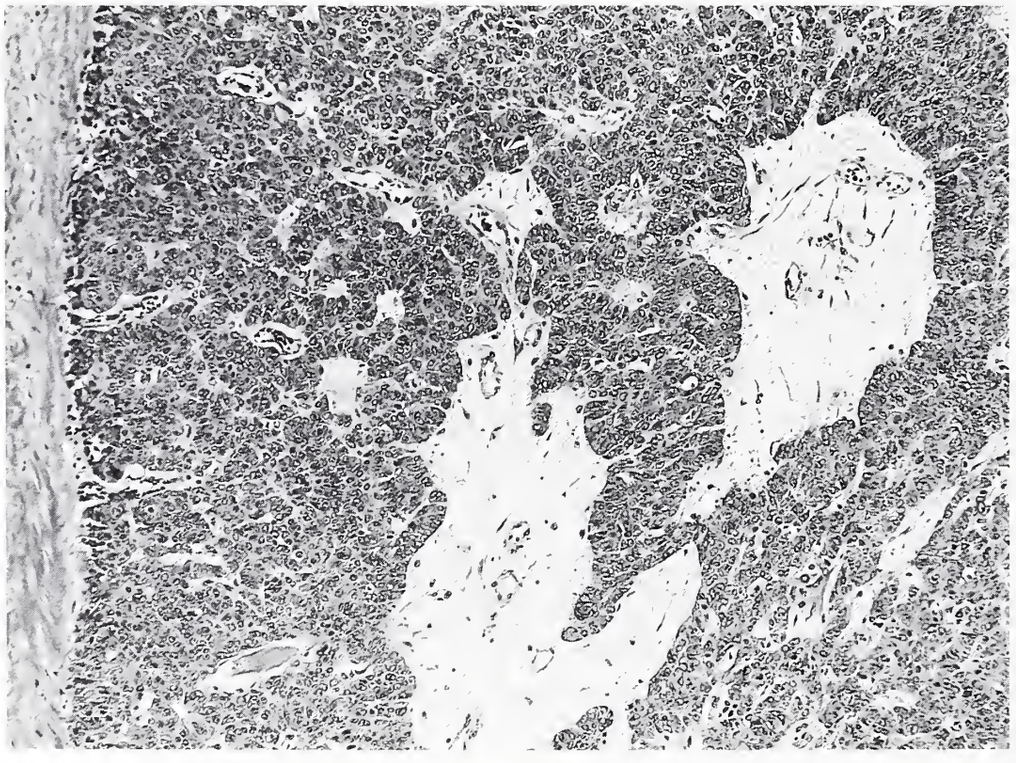
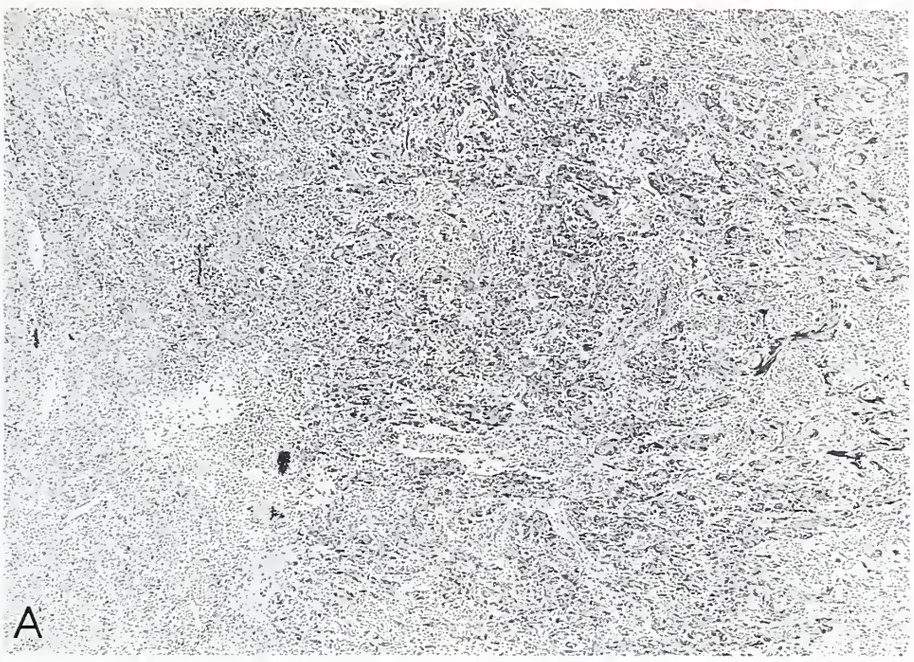
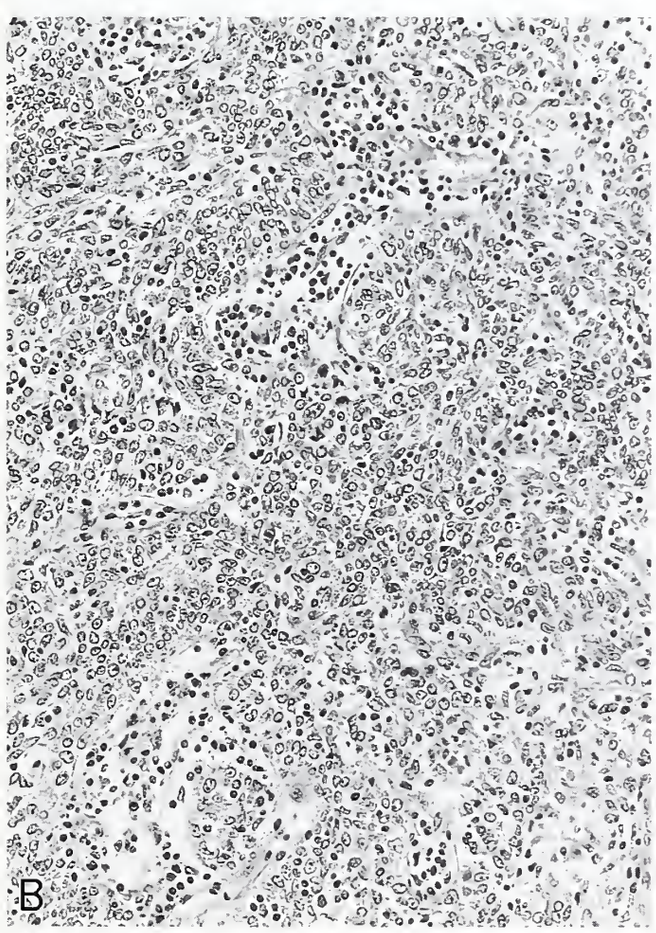


Figure 3-115
PROBABLE ORGANIZING PERIVASCULAR SPACE IN THYMIC CARCINOMA
In contrast to the hyalinizing stroma around the tumor nests, there are fine thin-walled blood vessels in loose fibroblastic tissue bordered by palisading cancer cells within solid nests and irregular anastomosing cords of carcinoma cells. This finding suggests early organization of perivascular spaces.





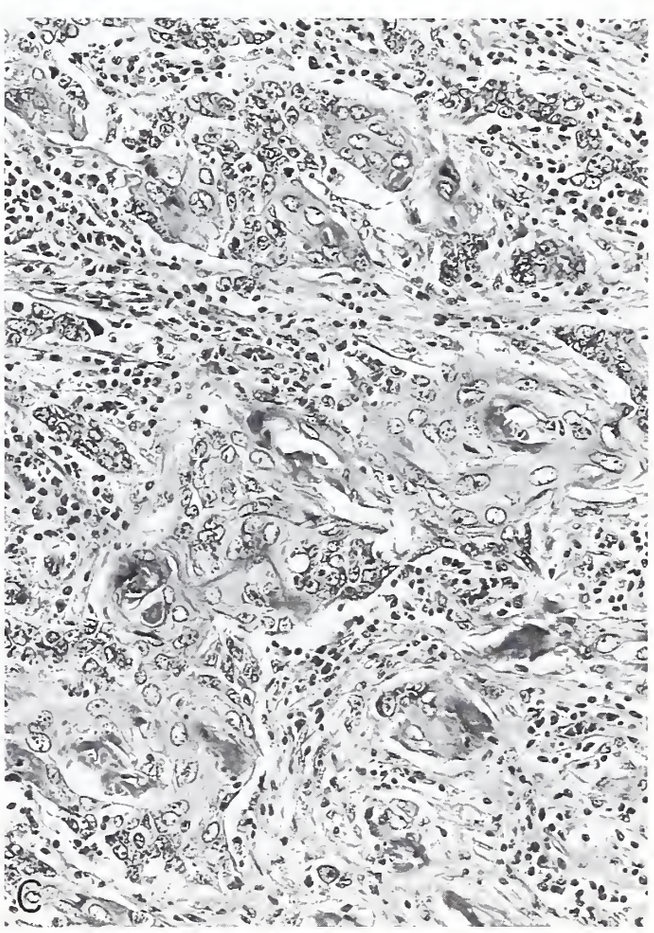


Figure 3-116

SQUAMOUS CELL CARCINOMA WHICH APPEARS TO HAVE ORIGINATED IN THYMOMA

A: A low-power view of the tumor, showing features of thymoma on the left and features of keratinizing squamous cell carcinoma on the right.

B: Higher magnification view of thymomatous area shows a mixture of lymphocytes and epithelial cells with bland nuclei and perivascular spaces with lymphocytes.

C: The same magnification of areas with keratinizing squamous cell carcinoma shows more evident individual cell atypia and rather marked keratinization (same case as that figure 3-107).

by radiotherapy at age 30, and recurrent tumor involving the right upper lobe of the lung and a subcutaneous and intramuscular tumor of the epigastric region corresponding to the site of mediastinal drainage from the previous surgical treatment were resected at age 36. All recurrent tumors were histologically similar, consisting of mixed lymphocytic and epithelial to predominantly epithelial thymoma with slightly atypical polygonal epithelial cells and small areas of epidermoid arrangement (fig. 3-117A,B). At the tumor border epithelial cells showed increased nuclear atypia and eosinophilic cytoplasm with a tendency toward keratinization, and were arranged in irregular, solid, infiltrating nests suggestive of poorly differentiated squamous cell carcinoma (fig. 3-117C,D) (Yasumasa Monden et al., unpublished case, 1995). Histologically, the tumor could be interpreted as an atypical thymoma displaying malignant progression to squamous cell carcinoma.

Two cases of thymic carcinoma involving the thyroid gland, reported by Mizukami et al. (135), can be classified as squamous cell carcinoma.

Basaloid Carcinoma. This is a rare thymic carcinoma, which is said to be of low-grade malignancy. We have seen only one case that fits the description in the literature.

Grossly, the tumors are solid with areas of hemorrhage and cyst formation, or are multilocular cystic. Our case was also partially cystic, and encapsulated (fig. 3-108). Microscopically, the tumors are composed predominantly of relatively small, uniform, spindle to polygonal cells with scanty cytoplasm, and round to oval nuclei with inconspicuous nucleoli; the cells are arranged in trabeculae and anastomosing cords. Tumor cells at the periphery of trabeculae show a radial arrangement or palisading similar to the patterns seen in basal cell carcinoma of the skin (fig. 3-118) (146,147). Differentiation towards squamous cells may be seen in small areas, as well as gland-like or cystic spaces. Mitotic figures are frequently seen.

A basaloid carcinoma with features suggestive of thymic cyst origin has been described (146). In our case, cuboidal cells lining the cysts were replaced by basaloid carcinoma (fig. 3-119).

Mucoepidermoid Carcinoma. This is also a rare subtype, and only a small number of cases have been reported so far. Grossly, the tumor is solid or cystic and may be encapsulated. Its cut surface is nodular with a granular or mucoid appearance (136,146).

Microscopically, tumor cell nests are separated by bands of fibrous stroma, and are composed of a mixture of three cell types (figs. 3-120, 3-121, top) (146). The most frequent cells are "intermediate cells," which are polygonal to short and spindle-like, and have a moderate amount of eosinophilic cytoplasm, round to oval finely granular nuclei, and inconspicuous nucleoli. The second cell type is larger than the first, and characterized by basophilic intracytoplasmic mucin displacing the nuclei eccentrically to give an appearance of goblet cells. These cells occasionally form small glandular spaces. Cytoplasmic mucin, glandular spaces, and small cystic spaces within solid nests stain with Alcian blue–periodic acid-Schiff (PAS) (fig. 3-121, bottom). The third cell type consists of squamous cells with a tendency for keratinization. Mitotic figures are hardly evident in any of these three cell types. The features described are consistent with the histology of mucoepidermoid carcinoma in other organs such as salivary glands and bronchi. The differential diagnosis includes epithelial cell–predominant thymoma with areas of mucin-producing cells.

At first, mucoepidermoid carcinoma of the thymus was included as a thymic carcinoma of low-grade malignancy (147). However, recent studies indicate that there is a wider histologic spectrum of differentiation, from well to poorly differentiated, and that the biologic behavior closely correlates with the degree of differentiation and cytologic atypia. Two patients with intermediate and high-grade tumors died within 2 and 7 years of initial diagnosis, four of six patients were between 17 and 26 years of age, and four tumors were closely associated with cystic structures having the features of acquired multilocular thymic cysts (136).

Adenosquamous Carcinoma. Carcinomas with combined squamous and glandular features uncharacteristic of mucoepidermoid carcinoma are placed in this category. Among squamous cell carcinomas of the thymus are cases with minor components of glandular differentiation in addition to the squamous component (fig. 3-122A,B). In routine practice, these components may be so minor that their presence is merely added descriptively to the main diagnosis of squamous cell carcinoma.

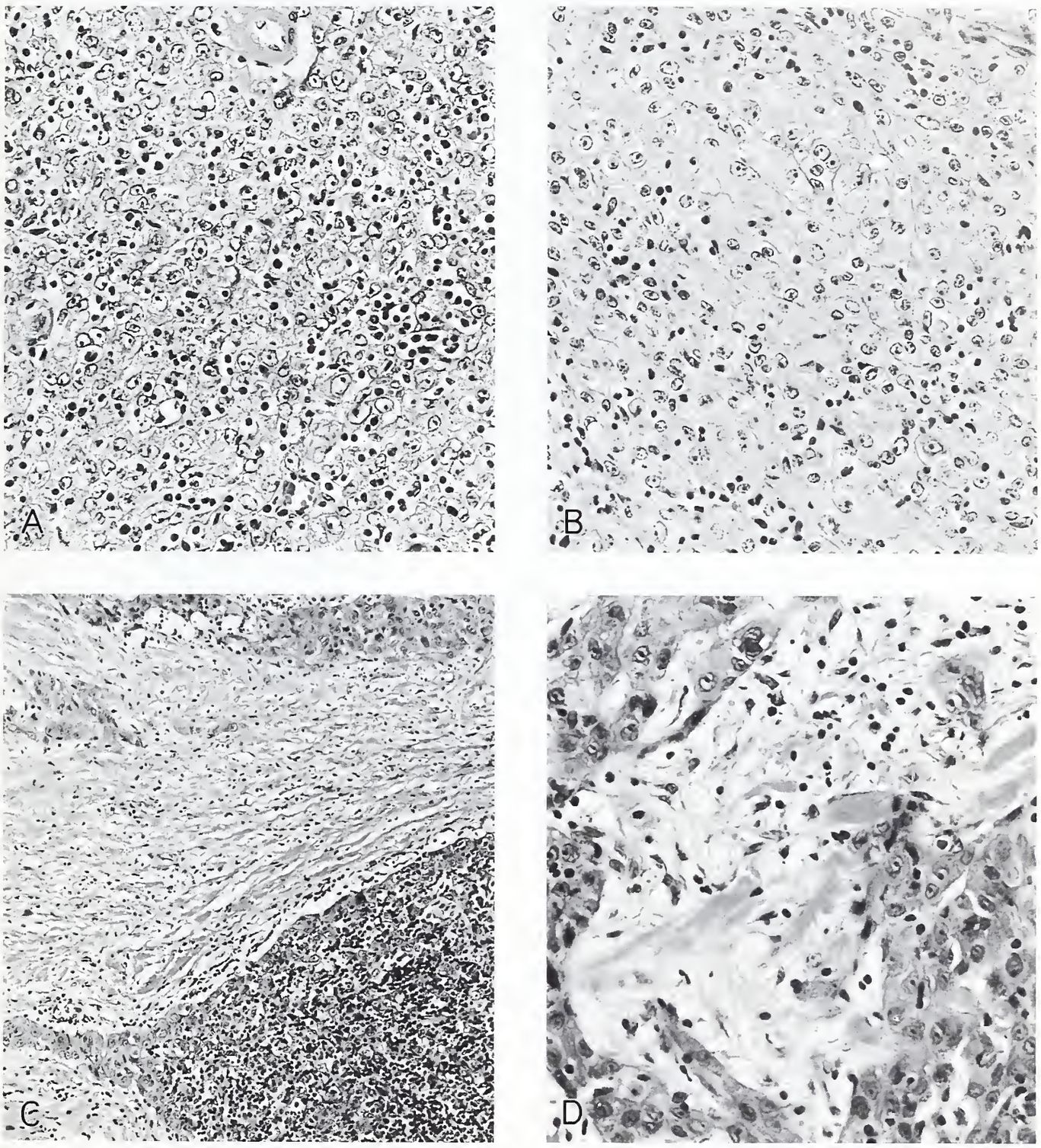


Figure 3-117

ATYPICAL THYMOMA PROGRESSING TO POORLY DIFFERENTIATED SQUAMOUS CELL CARCINOMA

A: Histology of a mixed lymphocytic and epithelial thymoma. Polygonal epithelial cells have vesicular nuclei with prominent nucleoli.

B: In small areas, the epithelial cells display epidermoid features.

C: At the border of the tumor, a small focus of carcinoma consisting of irregular infiltrating nests of polygonal cells with vesicular nuclei, moderately prominent nucleoli, and eosinophilic cytoplasm showing a keratotic tendency, is noted. This apparently arose from a lobule of thymoma.

D: Higher magnification of carcinoma. (Courtesy of Drs. Yasumasa Monden and Kazuya Kondo, Tokushima, Japan.)

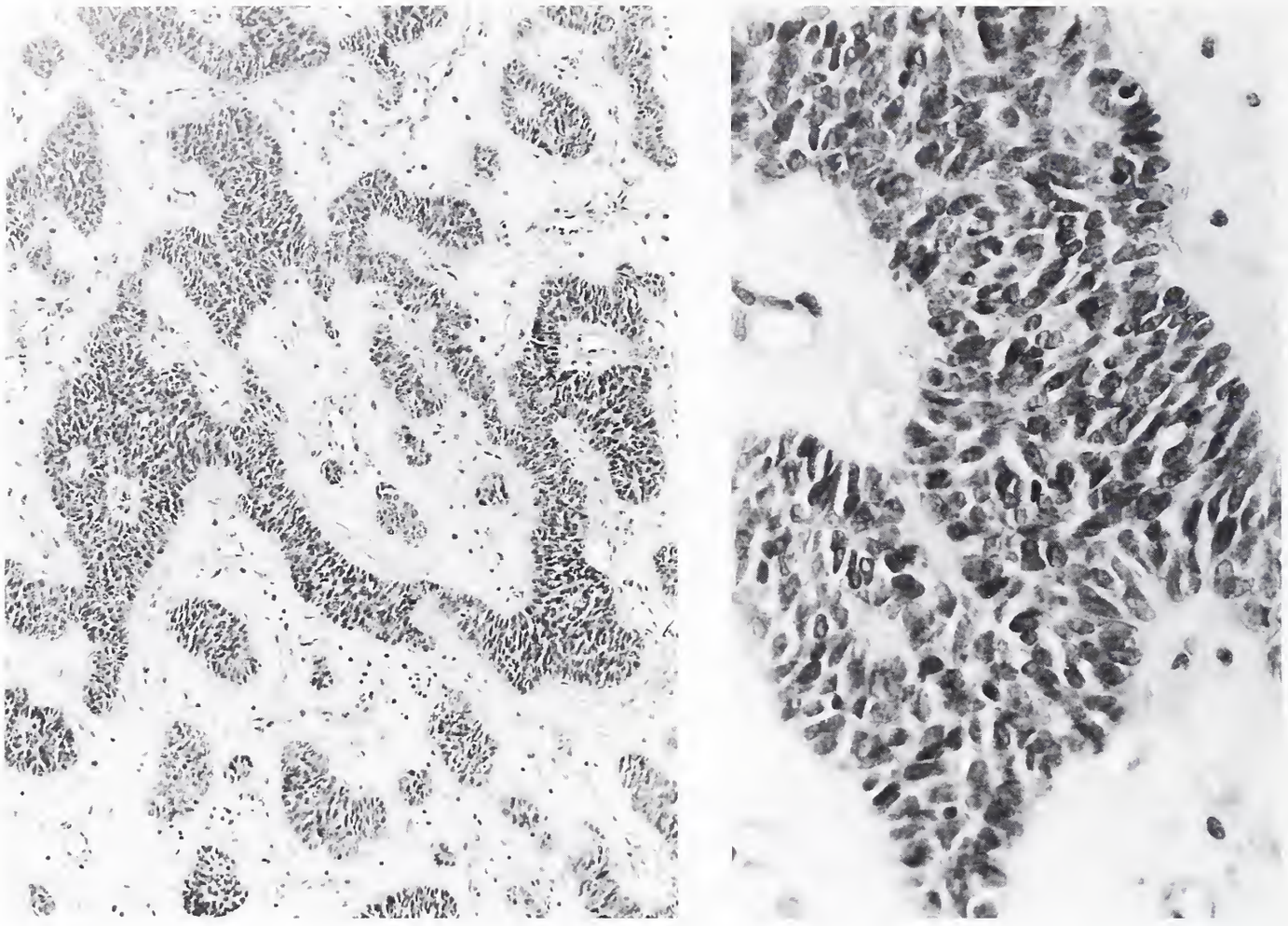


Figure 3-118
BASALOID CARCINOMA

Left: Palisading of cells at the periphery of tumor nests, trabeculae, and anastomosing cords is evident, resembling basal cell carcinoma of the skin.

Right: Higher power view. (Courtesy of Dr. Juan Rosai, New York.)

Histologically, tubular structures or small cystic spaces are found within the squamous cell nests, which may contain mucinous material, with occasional cellular debris that stains with alcian blue–PAS. Mucin-containing cells are few, if present. These small cystic spaces result from focal liquefactive degeneration of the tumor cells. However, immunostaining for a secretory component, which is considered to be a marker of glandular cells, reveals foci of aggregated, stained tumor cells (fig. 3-122C), indicative of glandular cell characteristics (132). Whether this entity should be diagnosed as adenosquamous cell carcinoma or squamous cell carcinoma with features of glandular cells is a matter of preference.

Preliminary studies indicate that patients with these tumors have a better outcome than those with pure squamous cell carcinoma (132). The rarer mucoepidermoid carcinoma may be considered a variety of adenosquamous carcinoma of the thymus.

Adenocarcinoma. In the literature, it was impossible to find a single authentic case of primary adenocarcinoma in the thymus or anterior mediastinum not associated with germ cell tumor, although combined adenocarcinoma, such as mucoepidermoid carcinoma and adenosquamous carcinoma, does develop in this organ. It is not unreasonable to expect adenocarcinoma to occur in the thymus because of the presence of intracytoplasmic mucin in the thymic epithelial cells making up both cystic and noncystic Hassall corpuscles and in isolated epithelial cells (118), and because of the presence of glandular structures in a few thymomas, which may or may not produce mucin.

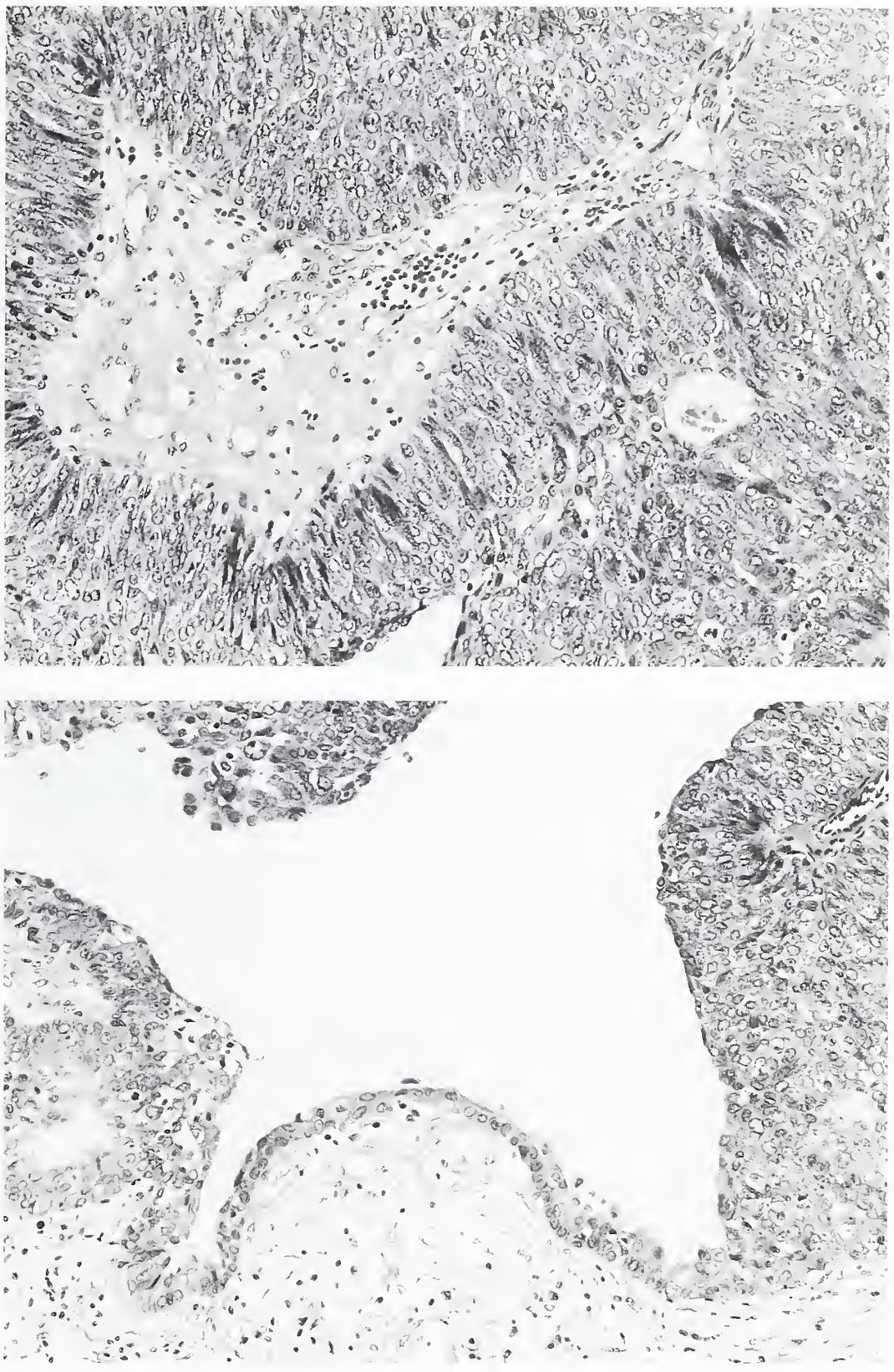


Figure 3-119
A TYPE OF BASALOID CARCINOMA

Top: Tumor cells facing a perivascular space and fibrous stroma surrounding the nest display pronounced palisading. The cellular arrangement is similar to that in basal cell carcinoma of the skin, but individual cell nuclei are vesicular rather than granular, simulating transitional cell carcinoma.

Bottom: Several cystic spaces were evident in the periphery of the tumor. They are lined by a few layers of much less atypical non-neoplastic cells, and are replaced in some areas by carcinoma cells (same case as that in figure 3-108).

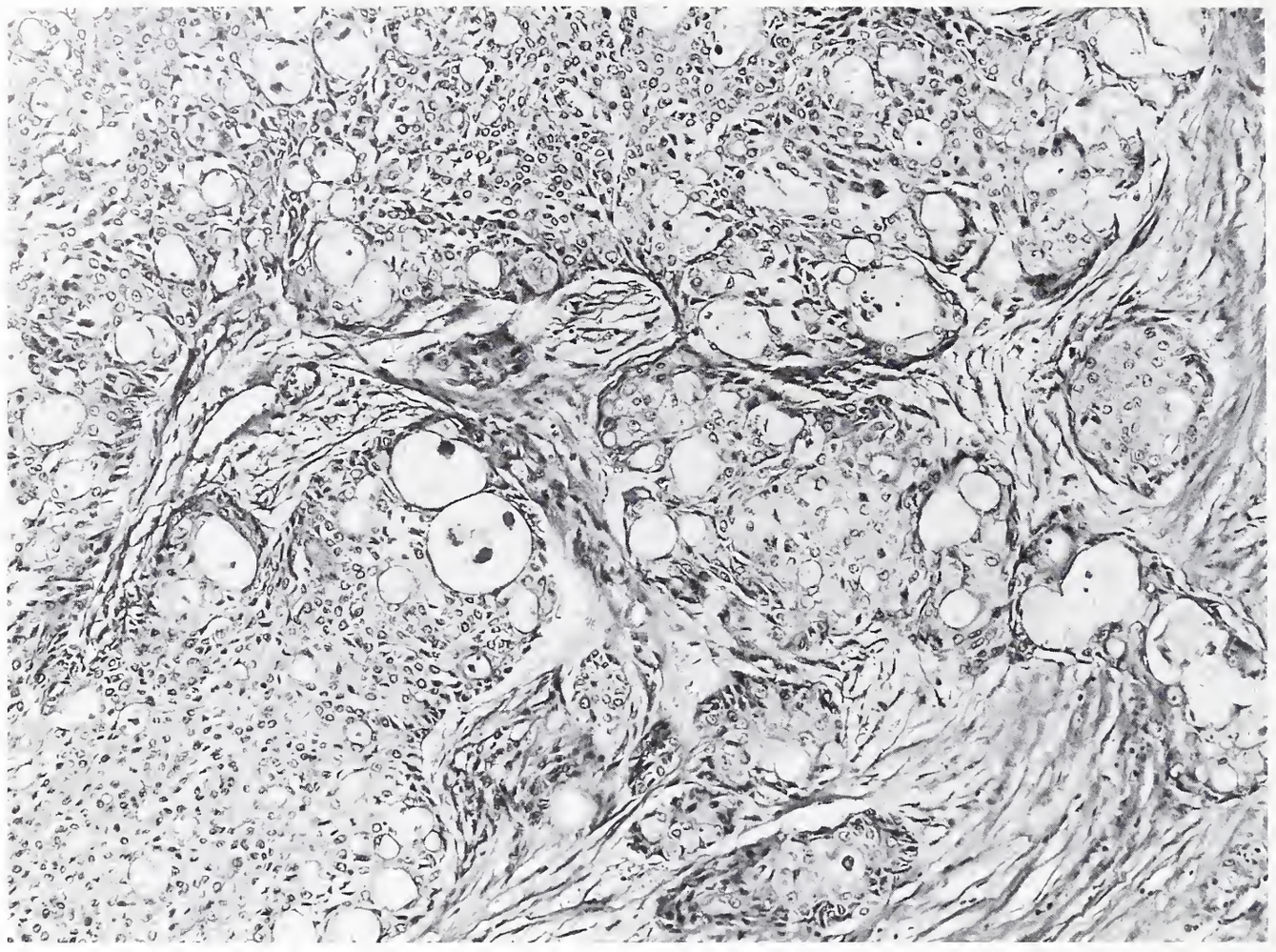


Figure 3-120
MUCOEPIDERMOID CARCINOMA
Tumor nests are composed of polygonal cells with a tendency to squamous cell differentiation and mucus-producing cells. Small spaces filled with mucus are also present within the nests. (Courtesy of Dr. Juan Rosai, New York.)

We recently saw two cases of papillary adenocarcinoma of the thymus, one displaying probable collision with thymoma and the other with partly solid growth. The differentiated portions of these two adenocarcinomas were similar. The case associated with thymoma was in a 70-year-old male, who was found to have a tumorous density in the anterior mediastinum on chest X-ray examination. Needle biopsy revealed adenocarcinoma which was thought to arise from a teratoma. The resected tumor was composed of two parts: a thickly encapsulated cystic thymoma and the other showing features of papillotubular adenocarcinoma with occasional psammomatous bodies resembling ovarian serous papillary adenocarcinoma. Small foci of necrosis were present and carcinoembryonic antigen (CEA) was focally positive immunohistochemically. Adenocarcinoma invaded the lung and its advancing border consisted of solid nests of poorly differentiated tumor cells. The thymoma was predominantly epithelial, of the short spindle cell type with no cellular atypia but with occasional small cystic spaces lined by flat to cuboidal cells and hemangiopericytoma-like areas. Collision between thymoma and carcinoma was noted within a thickly encapsulated nodule of thymoma (fig. 3-123). Whether this case represents collision tumor or adenocarcinoma arising in thymoma is a matter of conjecture. No teratoma or primary adenocarcinoma was found in other organs (Yoshihiro Matsuno et al., unpublished case, 1995).

Lymphoepithelioma-like Carcinoma. Lymphoepithelioma-like carcinoma may be associated with areas of squamous cell carcinoma. One of Wick's (155) cases was composed partly of ordinary epithelial thymoma and a case reported by

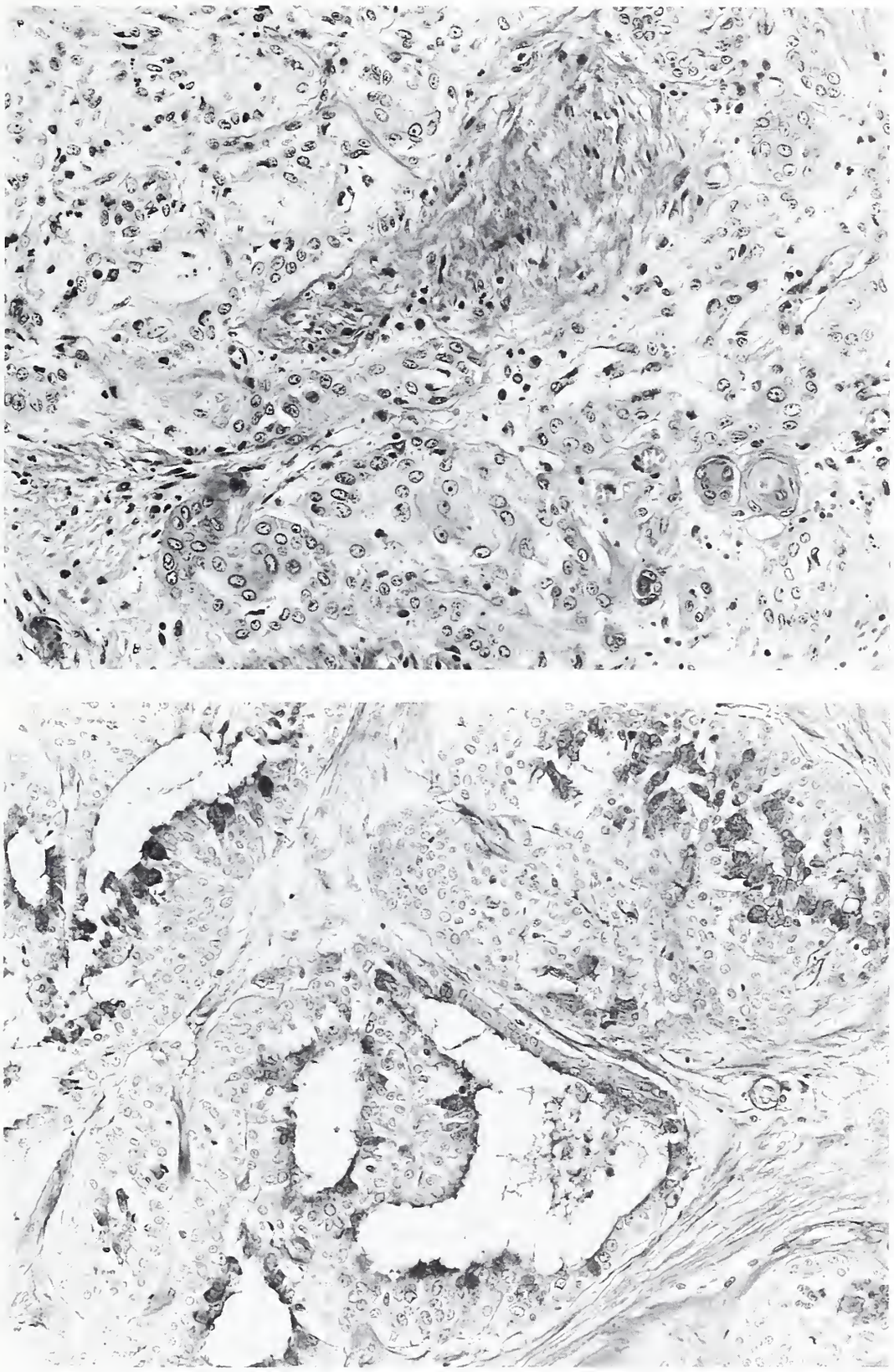


Figure 3-121
MUCOEPIDERMOID CARCINOMA

Top: This was an encapsulated, partly necrotic tumor consisting largely of intermediate cells. Here the tumor cells are arranged in acini lined by low columnar cells with clear cytoplasm and basal nuclei. In some areas the cells show epidermoid features with a keratotic tendency.

Bottom: Alcian blue–PAS staining reveals abundant mucin in the cytoplasm of the tumor cells forming the acini. (Courtesy of Dr. Tadaaki Eimoto, Nagoya, Japan.)

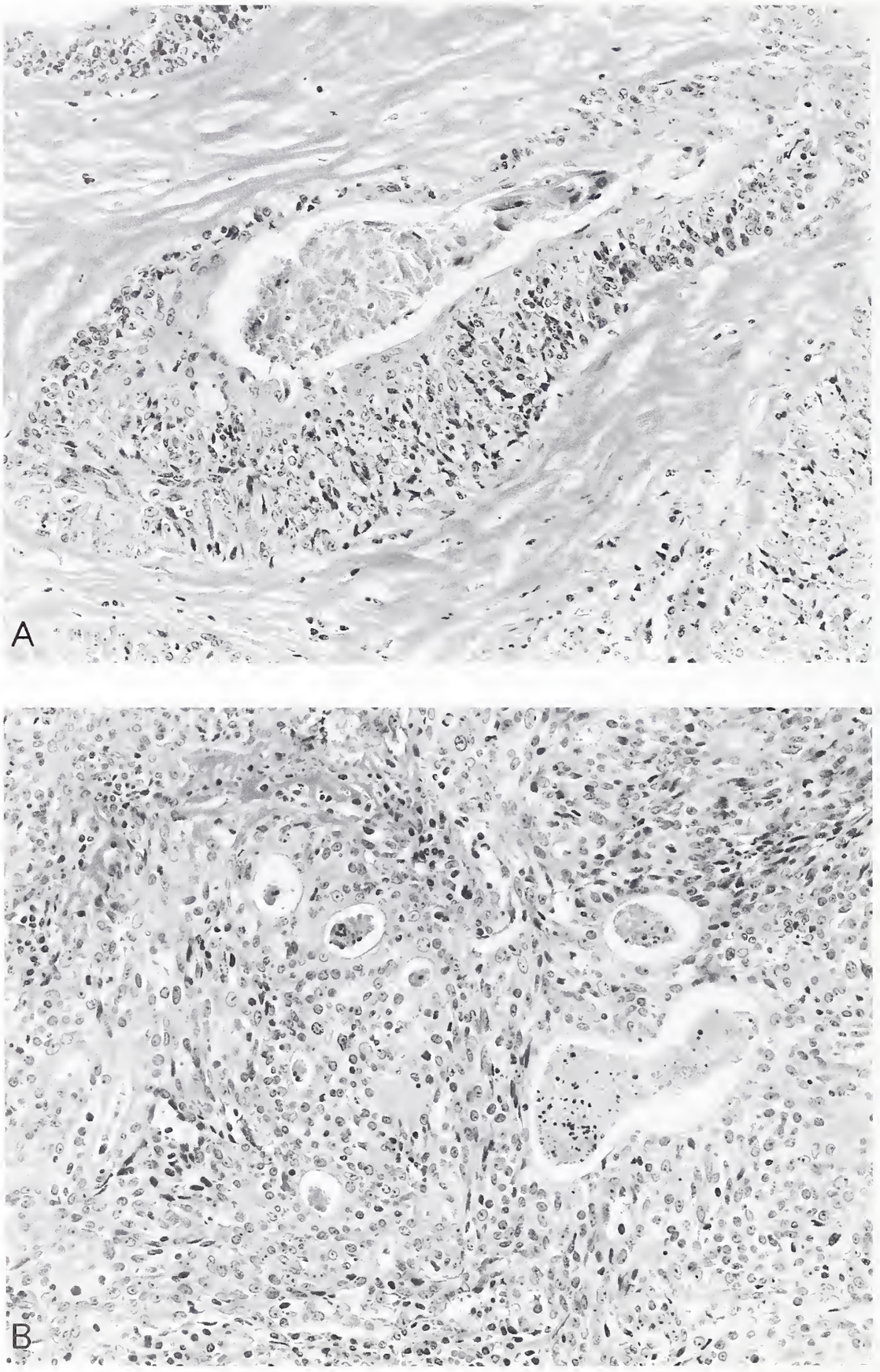


Figure 3-122
ADENOSQUAMOUS CARCINOMA
A: Solid nests of tumor cells surrounded by a hyaline stroma show keratinization.
B: Within a tumor nest are several tubular structures lined by low columnar to cuboidal cells with basal nuclei.

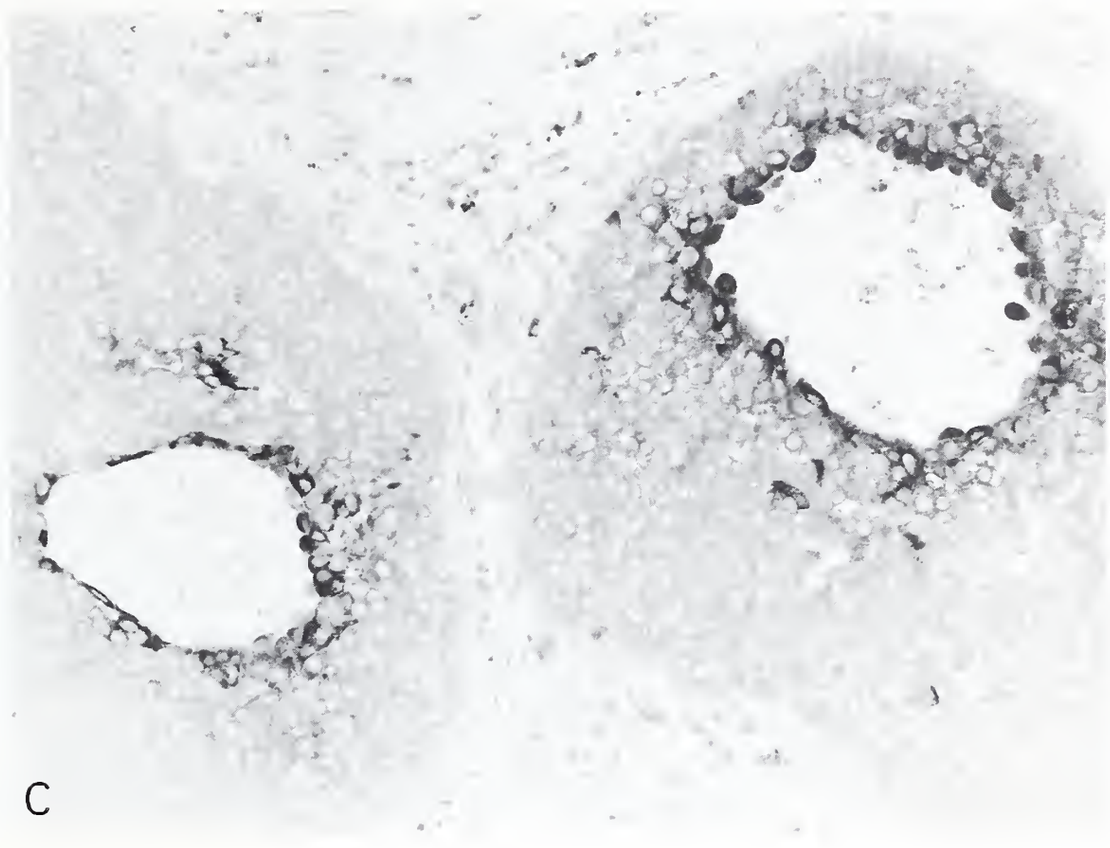


Figure 3-122 (Continued)

C: The cytoplasm of tumor cells facing a cystic space in a solid tumor nest stains for secretory component, a marker of glandular cells, even in the absence of demonstrable mucin-producing cells.

Kuo et al. (126) was composed partly of spindle cell thymoma. This tumor resembles undifferentiated (lymphoepithelioma-like) carcinoma of the nasopharynx. It is composed of large nests and diffuse growth of large polygonal cells with large vesicular nuclei, single prominent and round eosinophilic nucleoli, and scanty cytoplasm with ill-defined cell borders, infiltrated to various degrees with lymphocytes and some plasma cells (fig. 3-124). When lymphocytic infiltration is minimal, the histology may be interpreted by some as poorly differentiated squamous cell carcinoma (fig. 3-125). What looks like lymphoepithelioma-like carcinoma at the light microscopic level may reveal combined squamous and neuroendocrine differentiation at the ultrastructural level (155). The outcome of patients with this subtype is poor, and it is placed in the high-grade histologic group by Suster and Rosai (147). This subtype is seen in younger patients; one of our cases occurred in a 10-year-old boy, and the youngest patient reported was a 4-year-old boy. Association of Epstein-Barr virus is discussed separately.

Large Cell Carcinoma. Although cases are few in number, these are poorly differentiated tumors in which individual tumor cells are large and arranged in solid nests or have diffuse growth, but show no differentiation microscopically toward any specific cell type, such as squamous cells, mucus-producing cells, or small neuroendocrine cells (figs. 3-126–3-128). In the lung, such carcinoma is designated large cell carcinoma. Lymphoepithelioma-like carcinoma is considered to be a variety of large cell carcinoma. In the thymus, most large cell carcinomas are probably poorly differentiated squamous cell carcinoma ultrastructurally, but a few may be neuroendocrine in nature.

Small Cell/Neuroendocrine Carcinoma. Although a relatively high frequency of this subtype has been reported in the world literature, we have not seen any cases in our cancer hospital over the last 30 years.

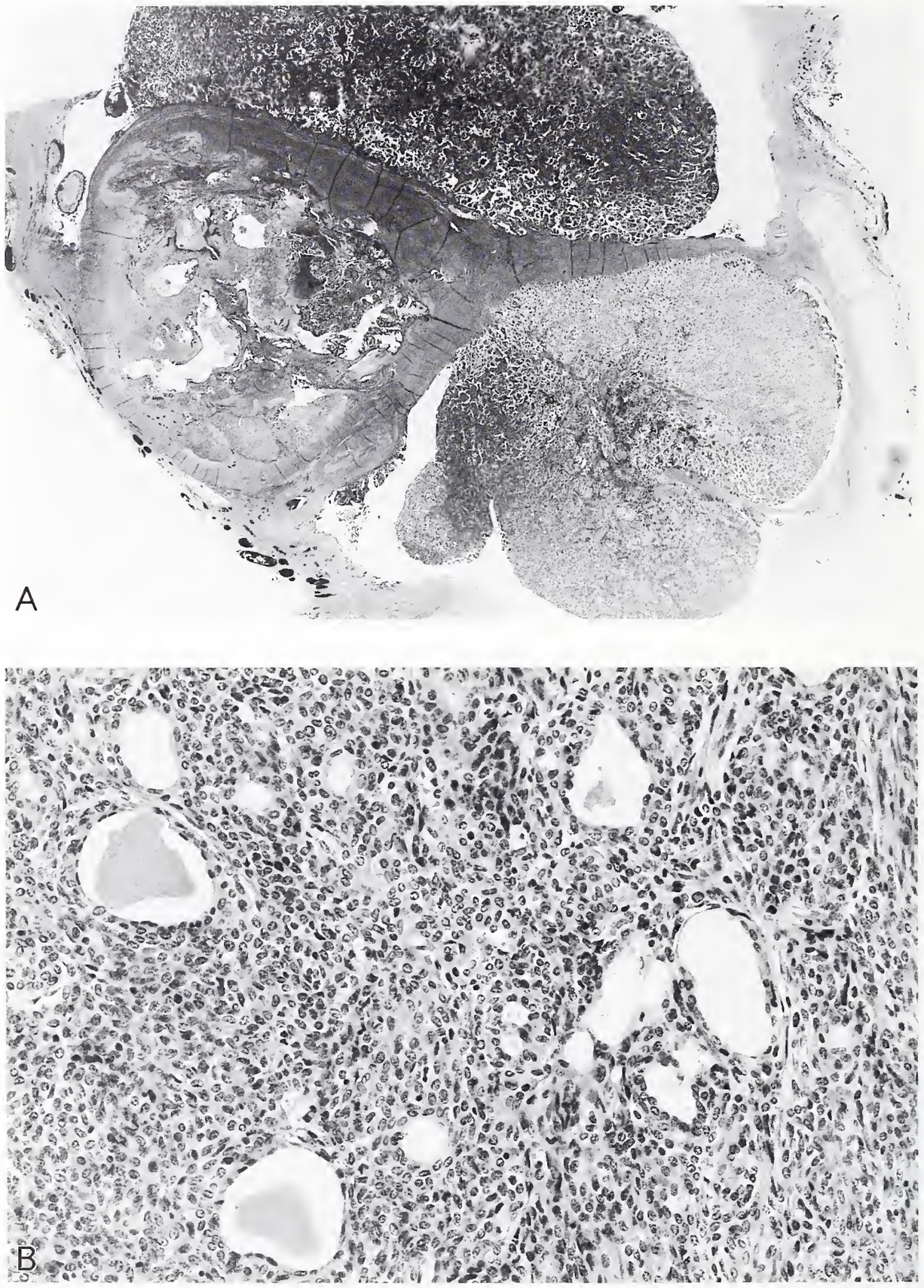


Figure 3-123
COMBINED PREDOMINANTLY EPITHELIAL THYMOMA AND PAPILLARY ADENOCARCINOMA

A: Low-power view of the tumor shows a thickly encapsulated cystic thymoma on the left and nodular, partly encapsulated tumors in the upper portion and right lower corner of the photograph.

B: Thymoma is partly cystic and composed of oval to short spindle cells with uniform nuclei.

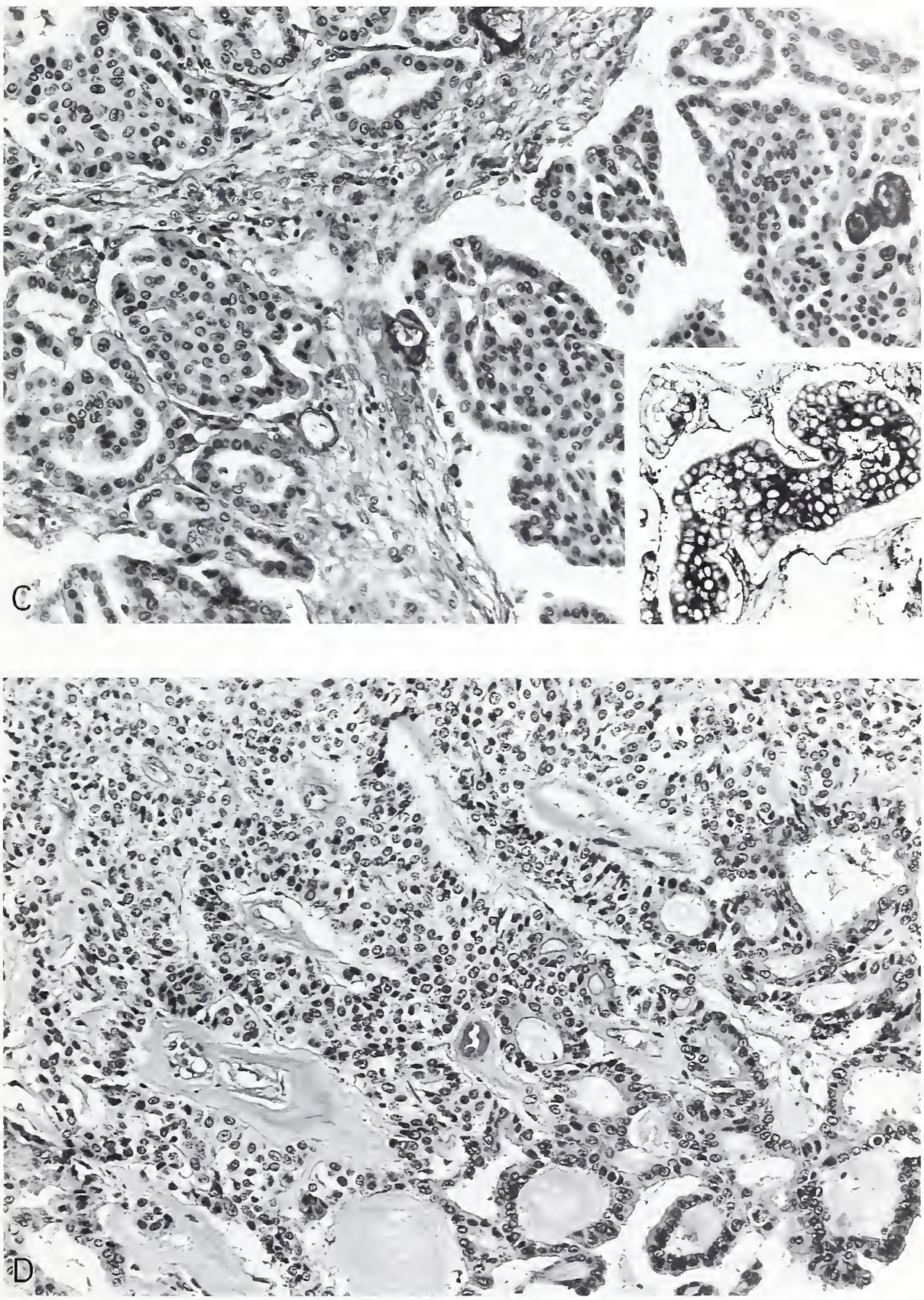


Figure 3-123 (Continued)

C: Histology of carcinoma showing a tubular and pseudopapillary arrangement with slight nuclear atypia and psammomatous bodies. Inset: Positive immunostaining of carcinoma cells for CEA.

D: Collision of thymoma and adenocarcinoma within the thickly encapsulated nodule (thymoma in the left upper corner and carcinoma in the right lower corner).

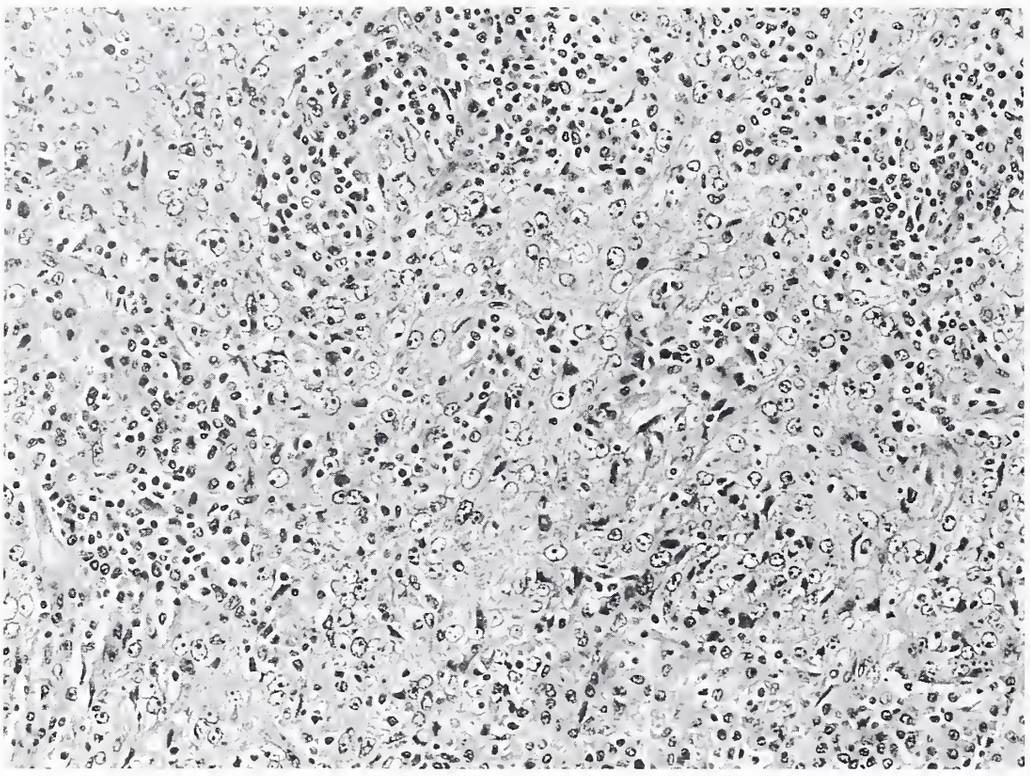


Figure 3-124
LYMPHOEPITHELIOMA-LIKE CARCINOMA

The tumor consists of geographic nests of polygonal cells with large vesicular nuclei and prominent nucleoli. The stroma is densely infiltrated by lymphocytes and plasma cells.

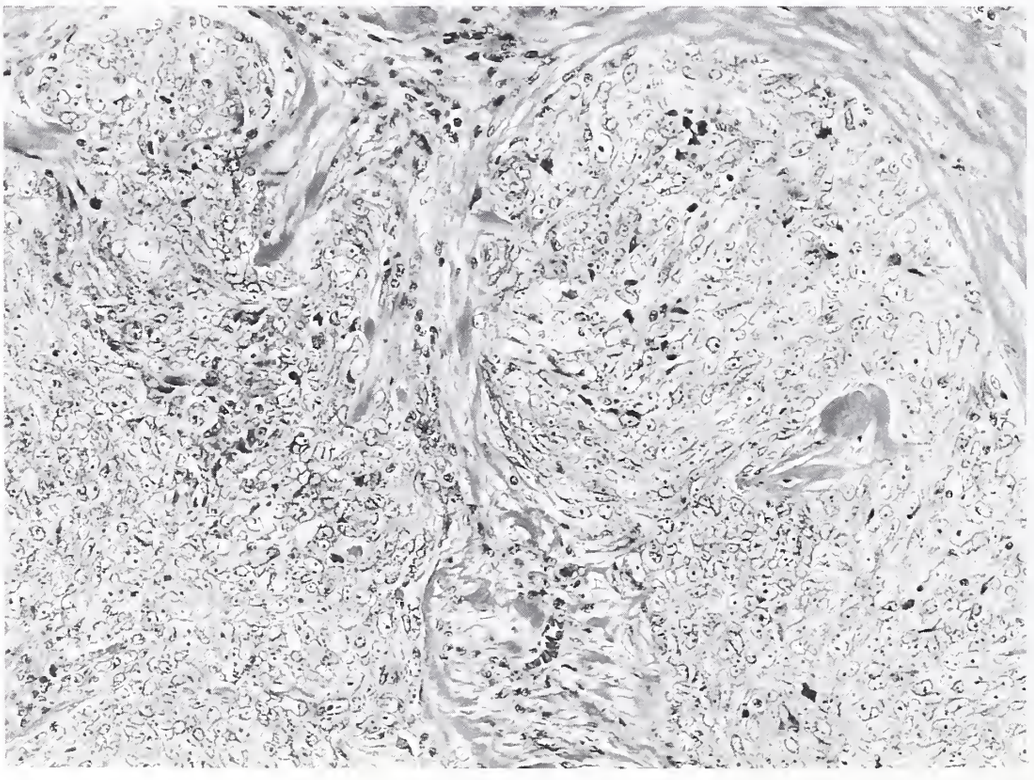


Figure 3-125
UNDIFFERENTIATED CARCINOMA PRESENTING A DIAGNOSTIC PROBLEM

The individual tumor cells are very similar to those shown in figure 3-124 (lymphoepithelioma-like carcinoma). However, because of the sparsity of lymphocytes, this tumor may be subtyped as poorly differentiated squamous cell carcinoma.

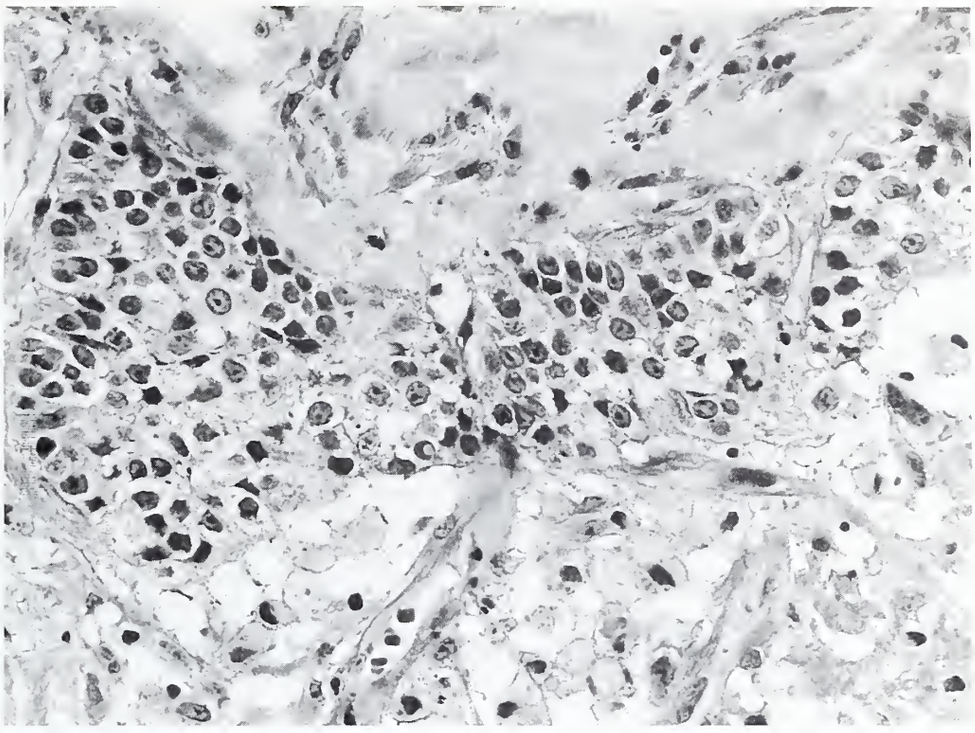


Figure 3-126
LARGE CELL CARCINOMA

The bulk of this tumor was necrotic, and only a thin layer of viable tumor cells remained at the extreme periphery. There are solid nests of polygonal cells with hyperchromatic nuclei and some prominent nucleoli. The lower portion of the field is occupied by foamy histocytes, which border an extensive area of coagulation necrosis.

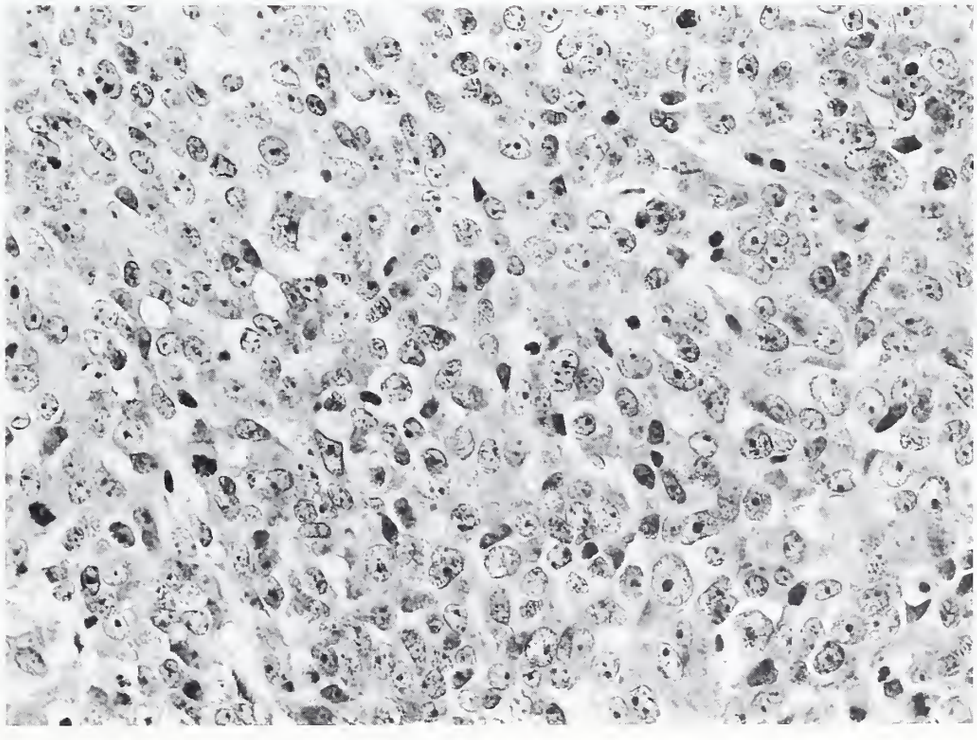


Figure 3-127
LARGE CELL CARCINOMA

This tumor shows diffuse growth of large polygonal cells with large round to oval nuclei having fine chromatin and single distinct nucleoli, a small amount of pale-staining cytoplasm, and ill-defined cell borders. There is no differentiation toward any particular cell type.

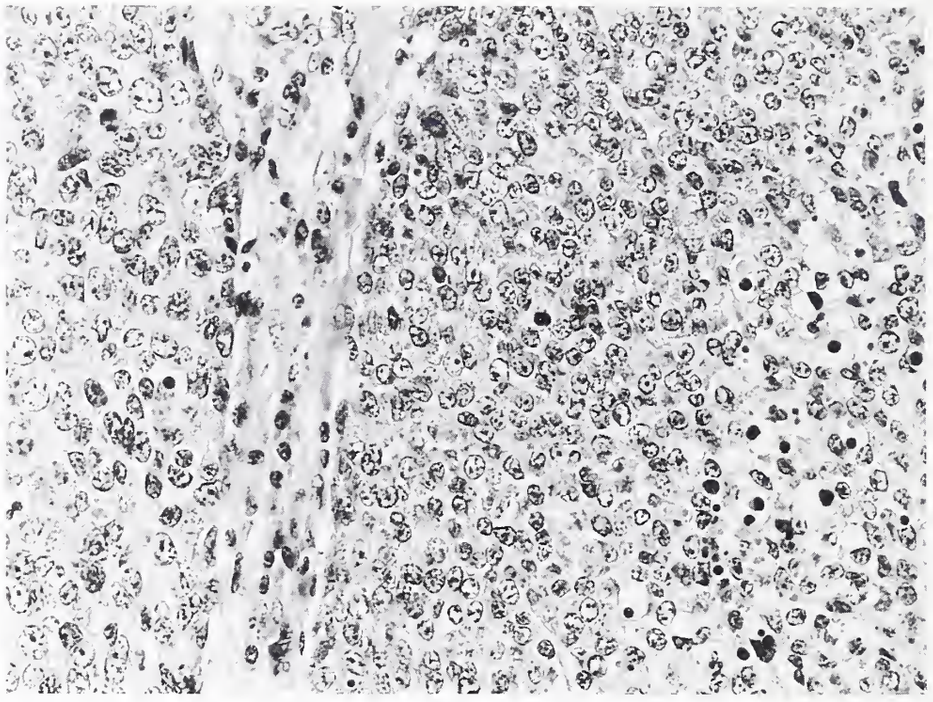


Figure 3-128
LARGE CELL CARCINOMA
In this tumor, although no definite keratinization or intercellular bridges are evident, the cellular details and arrangement suggest minimal squamous differentiation. Note the presence of many pyknotic cells in the center of a cell nest, and histologic similarity to the poorly differentiated squamous cell carcinoma shown in figure 3-114 (same case as that in figure 3-101).

This tumor is very similar to small (oat) cell carcinoma of the lung and may be combined with squamous cell carcinoma. It is characterized by diffuse growth and solid nests of small polygonal, oval to spindle cells with finely granular nuclei, inconspicuous nucleoli, scanty cytoplasm, and ill-defined cell borders (fig. 3-129). In some cases, tumors with features of small cell carcinoma have well-differentiated areas with a carcinoid histology (154,155). Neuroendocrine features presented in the literature include dense core granules of 100 to 200 nm or 200 to 500 nm in diameter depending upon the investigator, and the presence of immunoreactive neuron-specific enolase (NSE) (fig. 3-130). However, investigations of the neuroendocrine properties of this tumor are still insufficient, and no standardized definition of neuroendocrine carcinoma has yet been given.

Thus far, several neuroendocrine features have been studied in the lung and diffuse endocrine system; these include presence of cytoplasmic dense core granules, and immunoreactivity for NSE, Leu-7 (CD57), chromogranin A, synaptophysin, neural cell adhesion molecule (N-CAM), and brain-gut amine and peptide hormones (148–150). However, some of these features, such as NSE and Leu-7, are not specific to neuroendocrine cells, and are also present, although less frequently and with lower intensity or titer, in non-neuroendocrine tumors such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The "dense core granules" may not be neuroendocrine granules, but small lysosomes or exocrine granules. In order to prove that granules are neuroendocrine in nature, immunoelectron microscopy is necessary. Not only their morphology but also their location beneath the cell membrane or within cytoplasmic processes are important for identification in routine practice. Few amine and peptide hormones have been identified, including adrenocorticotrophic hormone (ACTH) in a case of thymic small cell carcinoma with Cushing's syndrome (141). Therefore, care must be exercised in the use of the term neuroendocrine carcinoma. Not only small cell/neuroendocrine carcinoma but also thymic carcinoid tumor should be further investigated with regard to function and possible correlations.

It has been reported that in contrast to the very poor prognosis of patients with small cell carcinoma of the lung, from which most patients die within 1 year after diagnosis, there is a much longer average survival time for patients with thymic small cell/neuroendocrine carcinoma. This indicates that the latter tumor is an entity different from small cell carcinoma of the lung, and biologically related to thymic carcinoid (155).

A combination of small cell carcinoma and squamous cell carcinoma appears to be more frequent in the thymus than in the lung. One of

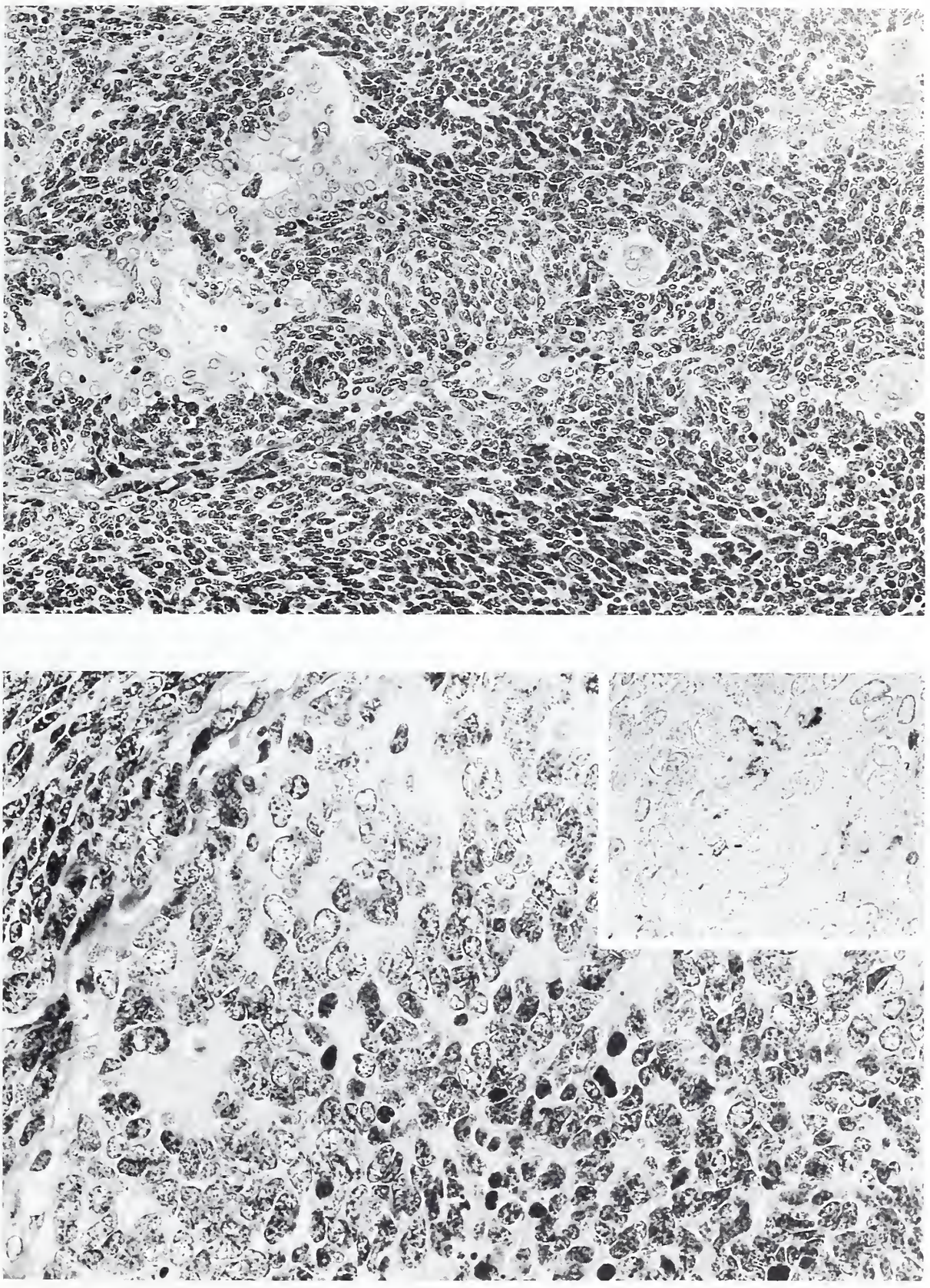


Figure 3-129
SMALL CELL CARCINOMA

Top: The tumor cells diffusely infiltrate and engulf the non-neoplastic thymic epithelial cells. They have scanty cytoplasm with ill-defined cell borders and nuclei with a finely granular chromatin pattern and inconspicuous nucleoli.

Bottom: A higher magnification reveals a few rosettes. Inset shows weakly positive immunostaining for synaptophysin. (Courtesy of Dr. Keiko Ishii, Matsumoto, Japan.)

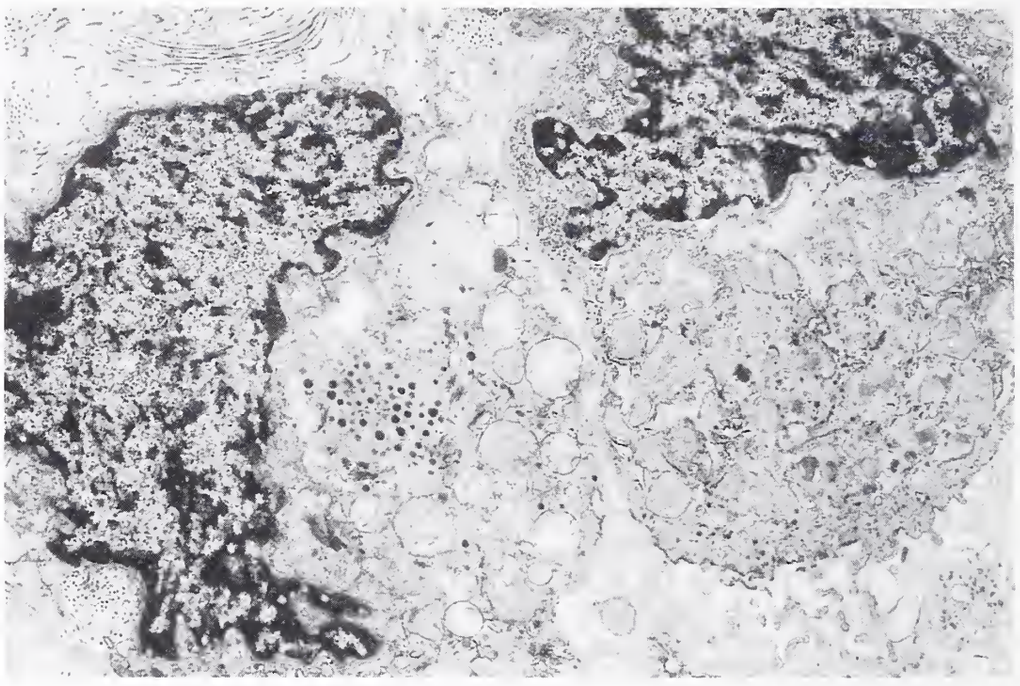


Figure 3-130
ULTRASTRUCTURE OF SMALL CELL CARCINOMA

Only a few tumor cells, as shown here, contained neurosecretory granules (X15,200). (Fig. 11 from Truong LD, Mody DR, Cagle PT, Jackson-York GL, Schwartz MR, Wheeler TM. Thymic carcinoma. A clinicopathologic study of 13 cases. Am J Surg Pathol 1990;14.151–66.)

four cases reported by Truong et al. (150), and all of three cases (two with squamous carcinoma and one with adenosquamous carcinoma) reported by Kuo et al. (126) were combined small cell carcinomas. Dense core granules are rare, and cases with positive immunohistochemical neuroendocrine markers are limited in number, suggesting that epithelial characteristics predominate over neuroendocrine characteristics in many thymic small cell carcinomas.

We have not seen a single case of small cell neuroendocrine carcinoma or mixed small cell undifferentiated squamous cell carcinoma, the histology of which is very similar to pulmonary oat cell carcinoma, at our institution. Apart from being rare, the incidence of thymic carcinoid may differ among races, and is probably very low in Asians or at least in Japanese. However, we have had three consultation cases of pure and combined small cell carcinomas. The first case was a 71-year-old female, who underwent total resection of 7.5 x 5.0 x 2.5 cm anterior mediastinal tumor (Masaoka stage II) followed by 50 Gy irradiation (tumor markers CEA, CA19-9, and SCC were within normal limits). Ten months later the patient developed multiple implantation metastases in the right pleural cavity with effusion, which contained tumor cells with features of small cell carcinoma. The NSE level in the pleural fluid was 40 ng/ml (normal, less than 10 ng/ml). There was no tumor in the lung. Histologically, the tumor was typical small cell carcinoma of oat cell type with a few rosettes, frequent mitotic figures, and small scattered foci of necrosis. In some areas, small nests of thymic epithelium were engulfed. Immunohistochemically, NSE was positive focally, synaptophysin was positive in a few cells, but cytokeratin, chromogranin A, gastrin-releasing peptide, and somatostatin were negative (fig. 3-129).

The second case was a surgically resected anterior mediastinal tumor showing limited invasion into the upper lobe of the lung. This tumor was composed of solid nests of small spindle cells, frequent rosette-like structures, and small areas with glandular spaces (fig. 3-131). Special stains disclosed an absence of epithelial mucin and the presence of immunoreactive NSE and secretory component. N-CAM and chromogranin A could not be demonstrated. Mitotic figures were easily found. This may have been a rare case of combined small cell carcinoma and adenocarcinoma of the thymus, considering the presence of atypical carcinoid tumor with frequent rosette-like and gland-like structures immunoreactive to chromogranin A, somatostatin, and alpha-human chorionic gonadotropin (see figs. 3-149, 3-153).

The third consultation case was a combined small cell and large cell carcinoma (fig. 3-132). The patient was a 66-year-old male, and the tumor was located in the anterior mediastinum, invading the left upper lobe of the lung, pericardium, and left

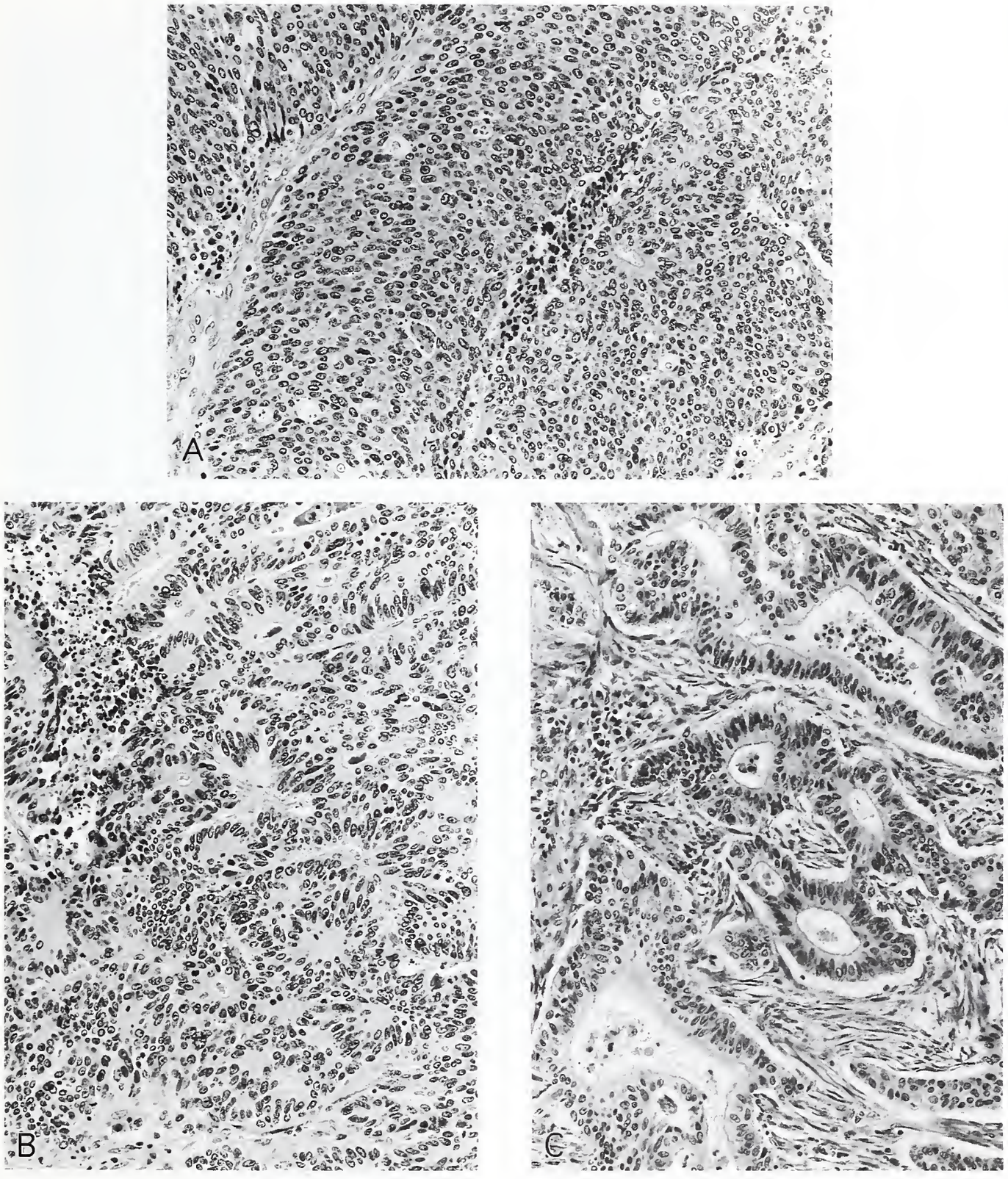


Figure 3-131

COMBINED SMALL CELL AND ADENOCARCINOMA OF PROBABLE THYMIC ORIGIN

A: Solid nests of the tumor consist of small short spindle cells with oval, finely granular nuclei and scanty cytoplasm, displaying a single rosette. The histology is similar to small cell carcinoma of the lung.

B: In some areas, frequent rosettes are present.

C: In a very small area, glandular structures lined by columnar cells are evident. Immunohistochemically, NSE was positive, but no other neuroendocrine markers were present, including N-CAM, chromogranin A, and synaptophysin. Alcian blue-PAS staining reveals no epithelial mucin, and only a glycocalyx is present at the luminal border of the cells. (Courtesy of Dr. Shinji Masuda, Takaoka, Japan.)

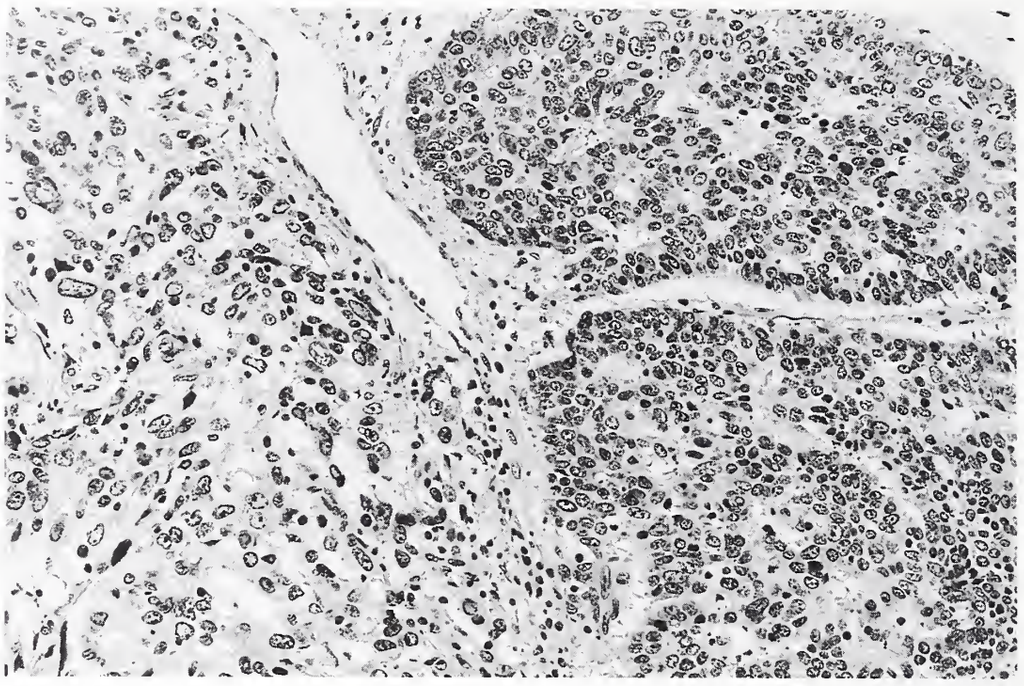


Figure 3-132
COMBINED SMALL CELL AND LARGE CELL CARCINOMA

Small cell carcinoma with rosettes is on the right and large cell carcinoma on the left. The area with small cell carcinoma shows characteristic finely granular nuclei, and that with large cell component vesicular nuclei with distinct nucleoli. (Courtesy of Dr. Yoshiro Tachiyama, Hiroshima, Japan.)

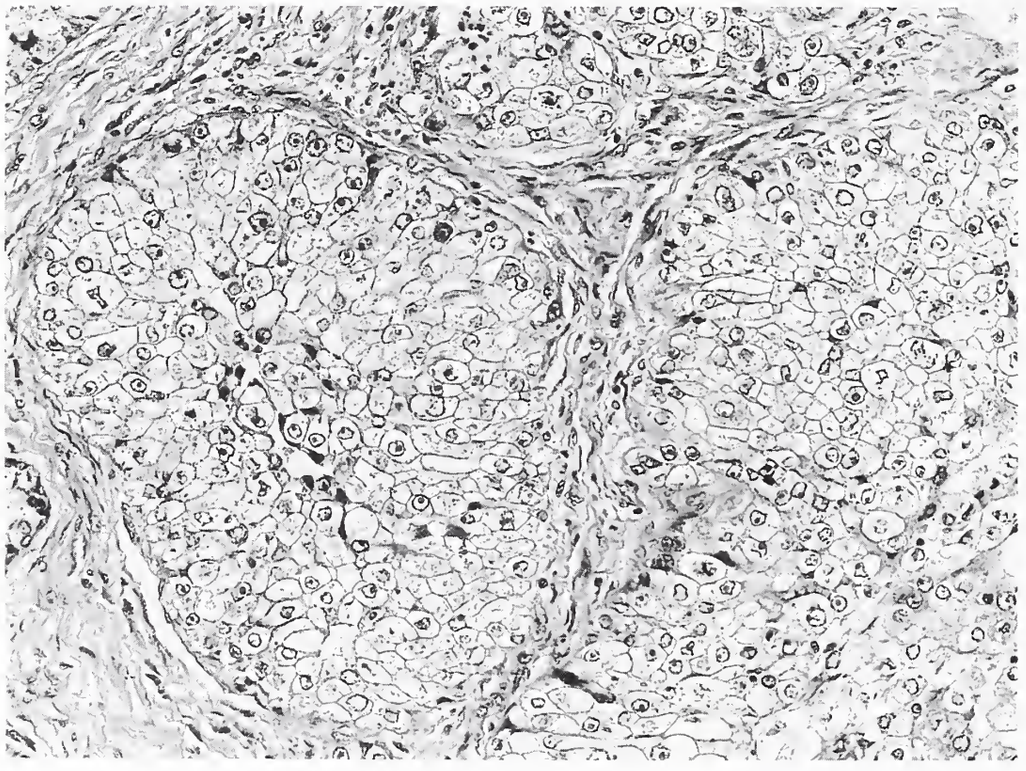


Figure 3-133
CLEAR CELL CARCINOMA

Solid tumor nests are composed of polygonal cells with abundant clear cytoplasm. (Courtesy of Dr. Hans Konrad Müller-Hermelink, Würzberg, Germany.)

brachiocephalic vein. Immunohistochemically, the tumor was positive for NSE and weakly positive for chromogranin A. Grimelius stain revealed no argyrophilia.

Clear Cell Carcinoma. This is also a rare subtype, but more cases have been reported in comparison with the mucoepidermoid and basaloid varieties.

Grossly, it is reported to be a solid tumor, consisting microscopically of lobules or sheets of polygonal cells with abundant clear cytoplasm, small nuclei with inconspicuous nucleoli or medium-sized vesicular nuclei with eosinophilic nucleoli, and a scanty fibrovascular stroma (fig. 3-133) (146). The clear cytoplasm contains abundant glycogen and some neutral fat but no mucin.

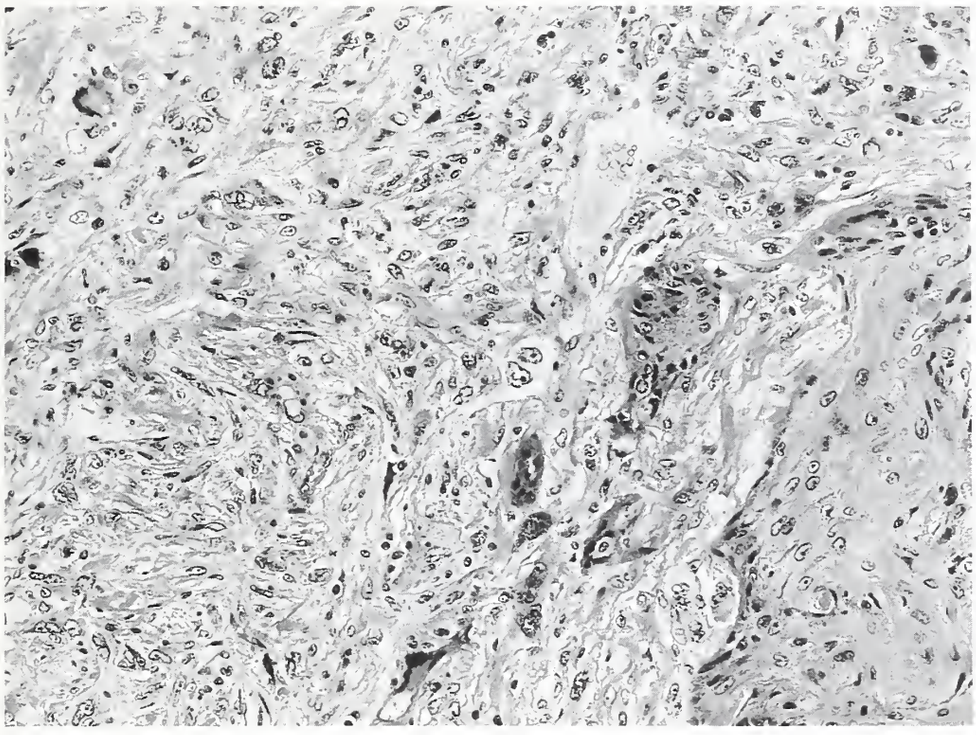


Figure 3-134
SARCOMATOID CARCINOMA
The tumor consists of solid nests of polygonal cells showing squamous differentiation, surrounded by spindle cells with nuclear atypia, and some bizarre tumor cells. There are no areas showing specific mesenchymal cell differentiation. (Courtesy of Dr. Tetsuro Kodama, Kashiwa, Japan.)

It may be included in the category of large cell carcinoma. Several cases studied by electron microscopy and immunohistochemistry were believed to be a form of squamous cell carcinoma in view of the presence of tonofibrils, desmosomes, and high molecular weight cytokeratin (150). Areas of necrosis and a few to occasional mitotic figures (0 to 5 per 10 high-power fields) were seen.

It is considered to be a tumor of high-grade histology in spite of its relatively slow growth in some cases. A recent review of the literature indicated that 9 of 13 patients (69 percent) either died of disease or had persistent disease at the time of follow-up (117). Differential diagnoses include metastatic clear cell carcinoma from other organs and predominantly epithelial thymoma with a clear cell component (see fig. 3-69).

Sarcomatoid Carcinoma (Versus Carcinosarcoma). This is also a rare subtype (146,155). We have seen one consultation case.

Grossly, the tumor is solid in part, and may be lobulated. Microscopically, there is diffuse growth of spindle cells with oval, coarsely granular nuclei and inconspicuous nucleoli, arranged in bundles, a storiform pattern, or haphazardly. Mitotic figures are frequently seen. Separated from and within the areas of spindle tumor cells are foci of larger polygonal cells with oval, somewhat vesicular hyperchromatic nuclei, some prominent nucleoli, and eosinophilic cytoplasm, displaying differentiation toward squamous cells (fig. 3-134).

This is a high-grade malignant tumor, with rapid growth and wide metastatic spread, resulting in short survival of patients. One tumor had rhabdomyoblastic differentiation with definite cross-striations and immunostaining for myoglobin (fig. 3-135) (146); cytokeratin was found not only in epithelial cells but also in the spindle cells. Based upon histology and immunohistochemistry, the name sarcomatoid carcinoma rather than carcinosarcoma seems justified; its morphogenesis is explained by the neoplastic metaplasia of the epithelial component to mesenchymal cells.

Immunohistochemical Findings. Immunohistochemical analysis of thymic carcinoma should be done for both epithelial cells and lymphocytes. Most antibodies described in this section are reactive with formalin-fixed, paraffin-embedded tissue unless otherwise stated.

Since thymic carcinoma is an epithelial tumor, it is natural to expect that every tumor will react with antibodies against cytokeratins of various molecular weights and epithelial membrane antigen. This is, in fact, the case. In nonsmall cell carcinoma, some tumors are reactive for CEA, B72.3, and Leu-7 (CD57), although positive cells are often few in number (150). The former two

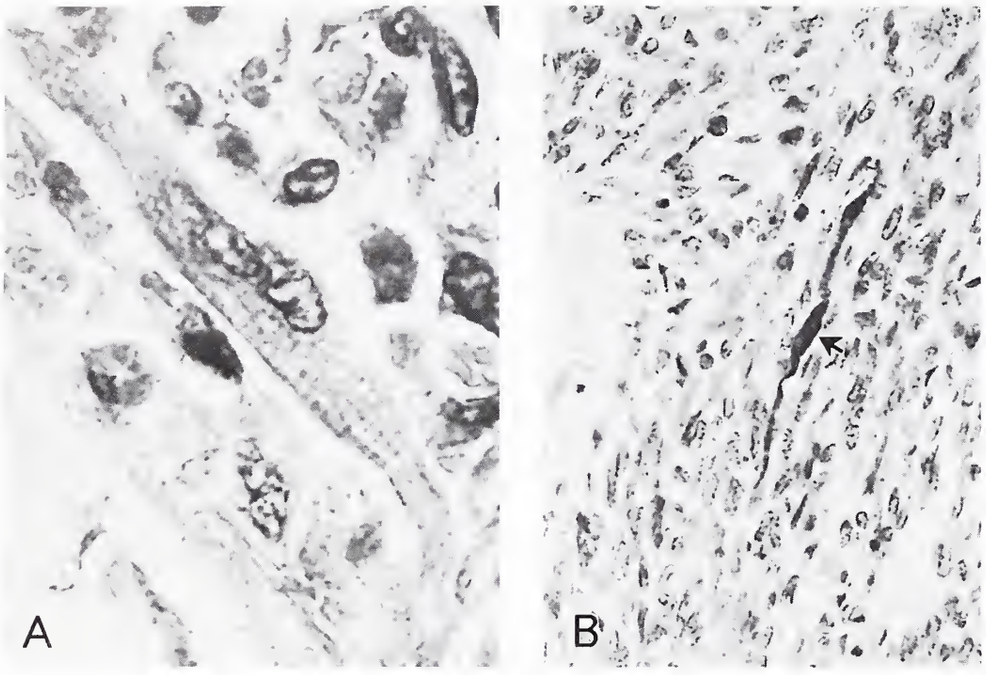


Figure 3-135
SARCOMATOID CARCINOMA WITH RHABDOMYOBLASTIC DIFFERENTIATION

Left: Cross striations are apparent in these elongated cells.

Right: Immunoperoxidase staining for myoglobin confirms the myoid nature of the cells (arrow). (Fig. 21 from Snover DC, Levine GD, Rosai J. Thymic carcinoma. Five distinct histological variants. Am J Surg Pathol 1982;6:451–70.)

markers are negative in thymoma and are thus used for differentiation. Leu-7 is positive in the majority of thymomas but entirely negative in squamous cell carcinoma, in our experience (123). Since well- to moderately differentiated adenocarcinoma of the lung as well as small cell carcinoma immunostain for Leu-7, this marker may be present in some forms of thymic carcinoma. Recently, Hishima et al. (119) reported that CD5, a type of receptor molecule that signals cell growth in T cells, was expressed immunohistochemically in epithelial cells of all of 7 thymic carcinomas, 2 of 5 atypical thymomas, but none of 11 typical thymomas or 43 carcinomas of other organs (119).

Müller-Hermelink and coworkers (130,138) divided thymoma into cortical, medullary, and mixed types according to the microscopic features of the epithelial cells. Their subclassification is said to be supported by results of immunostaining with several monoclonal antibodies, especially those against squamous epithelium keratin and surface phenotypes of T-cell lineage. The usefulness of such morphologic distinction of thymoma was questioned by some investigators (125). Moreover, Kirchner et al. (122) have recently proposed an entity of well-differentiated thymic carcinoma of low-grade malignancy, which was classified previously as cortical thymoma but exhibits a clear-cut predominance (over 50 percent of tumor tissue) of epithelial cell–rich areas with epidermoid differentiation (see figs. 3-47, 3-58). However, Kirchner's entity still shares not only common morphologic features but also a similar immunophenotype with cortical thymoma.

It has been reported that the small cell component of combined small cell and squamous cell carcinoma is positive for NSE (126). However, since NSE is not neuron specific in some other organs, the reactivity of other subtypes of thymic carcinoma should be tested. As far as can be determined, thymic small cell carcinoma, although called "neuroendocrine" by some, shows a lower frequency of neuroendocrine markers such as chromogranin A, Leu-7, and NSE than small cell carcinoma of the lung. No reports have mentioned the presence of N-CAM (neural cell adhesion molecule) or synaptophysin, and these should be further analyzed.

Analyses of surface phenotypes of infiltrating lymphocytes, for which either frozen sections of fresh tumor tissue or AMeX sections (142) should be used, reveal that immature T cells are always present in tumors that are diagnosed as thymoma. These cells are positive immunohistochemically for CD1a, CD3, CD4, and CD8, and for terminal deoxynucleotidyl transferase. However, infiltrating lymphocytes in thymic carcinoma possess surface markers of mature T cells, such as CD3+, CD1a-, and CD4 or CD8+, and the ratio of helper/inducer T cells to suppressor/

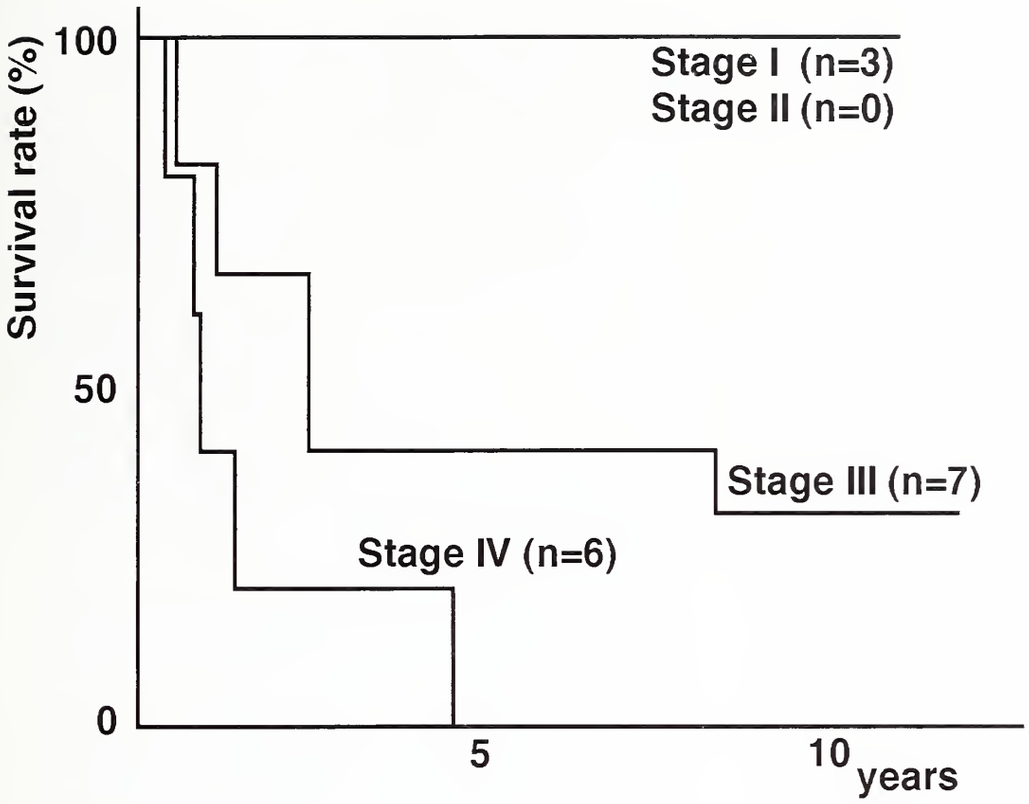


Figure 3-136
SURVIVAL CURVES OF PATIENTS WITH SURGICALLY RESECTED THYMIC CARCINOMA ACCORDING TO THE PATHOLOGICAL STAGING SYSTEM USED AT THE NATIONAL CANCER CENTER HOSPITAL
(Adapted from fig. 11 from Tsuchiya R, Koga K, Matsuno Y, Mukai K, Shimosato Y. Thymic carcinoma: proposal for pathological TNM and staging. Pathol Int 1994;44:505-12.)

cytotoxic T cells is the same as that seen in ordinary cancers of other organs (142). In other words, thymoma is a functional tumor with regard to migration from the bone marrow and maturation in the thymus of T cells, whereas thymic carcinoma has lost this function.

Müller-Hermelink and associates (122,130,138) have reported that some thymic carcinomas contain immature T cells. Their findings seem reasonable, because well-differentiated thymic carcinomas, by definition, are classified as predominantly epithelial thymoma with cell atypia.

The CD1a-positive cells seen in thymic epithelial tumors are not only immature T cells but also Langerhans cells or interdigitating reticulum cells. The latter are present both within tumor nests and the stroma, in clusters in areas showing medullary differentiation of thymoma, and scattered in other areas of thymoma and in thymic carcinoma (124). They can be demonstrated even after formalin fixation by immunostaining for S-100 protein. S-100 protein-positive small lymphocytoid cells are also found in thymic tumors.

Prognostic and Malignancy-Associated Factors. Prognostic factors in general include race, sex, age, immunologic status, performance status, therapeutic effects, TNM classification and stage, and factors associated with tumor malignancy. The last two are the most important for pathologists, and are assessed by relevant histologic, cytologic, molecular, and genetic factors.

TNM and Stage. TNM classification and stage are not malignancy-associated factors but indicators of tumor progression. Masaoka's classification of clinical staging is based on the study of thymoma, and is used widely. Recently, Masaoka and his group proposed a TNM classification of thymic epithelial tumors (Table 3-7) (113), the usefulness of which should be substantiated by further studies. An evaluation will be given by the Union Internationale Contre Cancer (UICC) in the near future. We use the TNM classification and staging scheme seen in Table 3-10 (151). Figure 3-136 shows survival curves of patients with thymic carcinoma treated surgically at our hospital using our new but tentative classification. From these survival curves, our classification appears to be applicable to both thymoma and thymic carcinoma for predicting patient outcome.

Histologic Types. At the histologic level, the most important prognostic factor is the histologic type of thymic carcinoma. Suster and Rosai classified thymic carcinoma into low-grade and high-grade groups, as mentioned already (Table 3-11). However, accumulation of the cases of

mucoepidermoid carcinoma, a tumor of low-grade histology, has shown that the prognosis correlates with the degree of differentiation and cellular atypia (136).

Squamous cell carcinoma of the thymus behaves less aggressively than that of the lung. A patient with thymic squamous cell carcinoma showing metastasis to the supraclavicular lymph nodes was cured by surgical resection and radiotherapy, and some tumors invading the lung were also cured by surgical resection and postoperative radiotherapy (145). Four of seven patients with squamous cell carcinoma reported by Truong et al. (150) were alive and well at 6 to 60 months postoperatively, while only three died of the disease at 7, 15, and 15 months. All six patients with pure squamous cell carcinoma reported by Kuo et al. (126) were alive for 13 to 43 months, one with disease, and every patient with well-differentiated squamous cell carcinoma among the consultation cases of Suster and Rosai (147) was alive. In contrast, the prognosis of patients with other histologic types, excluding rare low-grade mucoepidermoid carcinoma and basaloid carcinoma, is extremely poor; these tumors are classified as high-grade by Suster and Rosai.

Degree of Histologic Differentiation and Cell Atypia. Squamous cell carcinomas occurring in any organs are subdivided into well, moderately, and poorly differentiated categories. However, this classification has not been adopted for thymic carcinoma, probably because of its rarity. Our experience suggests that large cell or poorly differentiated squamous cell carcinoma without features of lymphoepithelioma-like carcinoma or with no small cell component shows marked proliferative activity and highly malignant behavior (see fig. 3-128). Such tumors should also be considered high grade. The dividing line between low- and high-grade squamous cell carcinoma needs to be investigated. In this regard, not only the degree of anaplasia and cell atypia but also the proliferative activity should be taken into account.

Lymphoepithelioma-like carcinoma is considered to be a poorly differentiated variety of squamous cell carcinoma, but its highly malignant nature, as in the case of small cell carcinoma, has been proved by every investigator.

Undifferentiated carcinoma of the nasopharynx (lymphoepithelioma-like carcinoma), however, can be cured by radiotherapy, even when metastasis is present in the superior cervical chain of lymph nodes. Therefore, if thymic lymphoepithelioma-like carcinoma can be treated at a sufficiently early stage, then cure may also be possible. Clear cell carcinoma and sarcomatoid carcinoma may also be considered a form of poorly differentiated squamous cell carcinoma. Subtypes may be rearranged in the near future for better classification. The degree of cytologic atypia and the proliferative activity, which can be expressed as the mitotic index (percent mitoses), are also important parameters associated with malignancy. In most cases, they are related to the degree of histologic differentiation: high-grade tumors often show marked individual cell atypia and increased mitotic activity.

Prognostic Factors at the Immunohistochemical Level. As described in the section on thymoma, diffuse expression in the cell membrane of beta-2-microglobulin, which is a light chain of human leukocyte antigen (HLA) class 1 antigen, was seen in 7 of 16 squamous cell thymic carcinomas as compared with only 2 of 17 thymomas, both of which were metastasizing "malignant" tumors. Similar findings were obtained for the HLA-DR alpha-chain. No cases of thymoma showed diffuse cell membrane staining, but 8 thymic carcinomas were diffusely positive. In other words, the expression of HLA antigens appears to be associated with the grade of tumor malignancy; however, no such study has been done on several subtypes of thymic carcinoma. The proliferating cell nuclear antigen (PCNA) positivity rate is a good indicator of malignancy in many organs, and this is also expected to be the case in thymic carcinoma.

Nuclear DNA Content and Histogram. As described with thymoma, cytofluorometric analysis of the nuclear DNA content of tumor cells disclosed a significant difference between thymoma (2.46 ± 0.18C in noninvasive and 2.63 ± 0.28C in invasive thymoma) and thymic squamous cell carcinoma (3.82 ± 0.98C) (see fig. 3-98). Aneuploid stem cell lines were seen in none of 13 noninvasive thymomas, only 1 of 13 invasive thymomas, and 12 of 13 thymic squamous cell carcinomas. Therefore, thymoma and thymic squamous cell carcinoma can be differentiated using a combination of mean nuclear DNA content and the presence of aneuploid stem cell lines (114).

Thus far, such studies have not been done among subtypes of thymic carcinoma. However,

such analysis, together with studies of histogram patterns of DNA contents, are expected to be useful for separating low-grade and high-grade tumors. The difference in mean nuclear areas of noninvasive thymoma, invasive thymoma, and thymic carcinoma (49.27 ± 7.88, 62.44 ± 5.10, and $76.79 \pm 10.27\ \mu m^2$, respectively) was statistically significant ($P<0.01$), although there were certain overlaps between the groups (see fig. 3-97) (114).

Prognostic Factors at the Genetic Level. Abnormalities in some oncogenes and tumor suppressor genes are considered to affect the prognosis of patients. Examples are amplification of N-*myc* and c-*erb*B2 in neuroblastoma and breast carcinoma, respectively, and point mutation of p53 in lung and other cancers (120,144,152). Malignancy-associated genetic changes have not yet been reported in thymic carcinoma, but probably will be in the near future, since paraffin blocks can be utilized for analysis in some instances.

Differential Diagnosis and Morphologic and Functional Correlation. Distinguishing thymic carcinoma morphologically from more common thymoma of the encapsulated and invasive (type I malignant thymoma) types includes assessing not only gross features, histologic structures, degree of cytologic atypia, and proliferative activity, but also immunohistochemical analysis of both epithelial cells and lymphocytes to clarify cell type, proliferative activity, and function, particularly T-cell maturation. Recent sophisticated assessment methods include determination of the nuclear DNA content of epithelial cells and its histogram pattern for evaluation of aneuploid stem lines. Abnormalities in genes may be revealed in the near future.

By our definition, thymoma is grossly characterized by either complete or incomplete encapsulation, lobulation, and no or minimal coagulation necrosis. In thymic carcinoma, encapsulation is rare and appears limited to certain histologic types such as basaloid carcinoma, although a capsule-like structure may be seen where the tumor reaches the capsule of the thymus, pleura, or pericardium. The borders of carcinoma are usually irregularly nodular or scalloped as a result of invasive growth. Lobulation does not occur or is inconspicuous, and areas of coagulation necrosis vary in amount depending on the type of carcinoma. Cystic changes are evident in both thymoma and carcinoma. Calcification may be present in the capsule of thymoma, but is almost always absent in carcinoma.

Histologically, thymoma is frequently lobulated by bands of collagenous tissue, shows a mixture of epithelial cells and varying numbers of lymphocytes, and often has easily recognizable widened perivascular spaces. However, none of these findings are specific to thymoma. For example, a mixture of lymphocytes is seen in lymphoepithelioma-like carcinoma, and large perivascular spaces in rare thymic carcinoma (figs. 3-115, 3-119, top). Characteristic histologic features in carcinoma include apparent invasive growth (fig. 3-112), arrangement of tumor cells in solid nests, foci of necrosis and hemorrhage, and varying degrees of lymphoid cell infiltration in the stroma.

Cytologically, the epithelial cells of many thymomas possess bland normochromic nuclei, with or without small round nucleoli, and have no or only a few mitotic figures. However, some thymomas with cellular atypia, which are classified as cortical thymoma and well-differentiated thymic carcinoma by Marino and Müller-Hermelink, Kirchner et al., and Quintanilla-Martinez et al. (122,130,140), reveal plump hyperchromatic nuclei and distinct round nucleoli, similar to those seen in carcinoma. Frequent mitotic figures, up to 10 or more per 10 high-power fields, may be seen, but no abnormal mitoses are observed unless irradiation has been performed. With regard to mitotic figures, the cell type should be distinguished, since lymphocytes in thymoma also reveal mitotic activity. Cell size may be of help in making the distinction, which can be confirmed by immunostaining for epithelial cell markers such as cytokeratin and surface phenotypes of lymphocytes by CD3 and UCHL-1 on frozen and paraffin sections, respectively.

Immunohistochemically, although CD57 (Leu-7) is often positive in thymoma and negative in squamous cell carcinoma, epithelial cell markers are not very useful for distinguishing the two tumor types since they may be positive in other types of carcinoma as well, such as small cell neuroendocrine carcinoma. The most important immunohistochemical findings for the differential diagnosis are the presence of immature (or cortical) T cells in thymoma and their virtual absence in thymic carcinoma. This finding indicates maintenance of the function of the thymic epithelium

in thymoma and loss of this function in cancer. The absence of myasthenia gravis as a complication in patients with thymic carcinoma is probably related to this loss of function. The presence of immature T cells in well-differentiated thymic squamous cell carcinoma, reported by Kirchner et al. (122), is due to the difference in histologic criteria of thymic carcinoma. The presence of these cells in predominantly epithelial thymoma may be difficult to prove, but the distribution of T-cell subsets in thymic carcinoma is similar to that in cancers of other organs, consisting of either CD8+ or CD4+ mature T cells.

The nuclear DNA content of the two types of tumors has been described previously: aneuploid cell lines are rare in thymoma but common in thymic carcinoma.

In rare cases, the differential diagnosis is difficult. This is expected, since in any organs, tumors on the histologic borderline between adenoma and carcinoma occur. Diagnosing the thymic epithelial tumors as either thymoma or thymic carcinoma is difficult if there is a mixture of lymphocytes and epithelial cells with probable perivascular spaces or fine vasculature within aggregates of tumor cells (fig. 3-112, top), or if epithelial cells, outnumbering lymphocytes, display some nuclear atypia and proliferative activity (see fig. 3-51). In cases where thymic carcinoma develops from thymoma, features transitional between the two may be observed, and the histology may be difficult to interpret. In such cases, immunohistochemistry for lymphocyte surface markers helps in the diagnosis. If this is not possible, the presence of plasma cells and eosinophils favors a diagnosis of carcinoma.

Distinction of thymic carcinoma from atypical carcinoid may be difficult at times, since the latter with moderate nuclear atypia, proliferative activity, and lack of typical features of carcinoid tumor such as rosettes may simulate poorly differentiated carcinoma (see fig. 3-146C). In such cases, Grimelius silver staining and immunostaining for neuroendocrine markers are essential for diagnosis.

Differentiation from germ cell tumors is another consideration. Particularly, care should be exercised when establishing a diagnosis on the basis of a needle biopsy specimen. Dysgerminoma with minimal lymphocytic infiltration and embryonal carcinoma may mimic poorly differentiated or undifferentiated carcinoma, and choriocarcinoma may resemble poorly differentiated squamous cell carcinoma (see fig. 3-174). In such cases, immunohistochemical staining for placental alkaline phosphatase and beta-human chorionic gonadotropin must be done. The marked male predominance of malignant germ cell tumors should be borne in mind.

Diffuse large cell lymphoma with sclerosis may resemble undifferentiated carcinoma histologically; the latter can be differentiated by immunostaining for B-cell markers (see figs. 3-207, 3-209) (115,139).

In routine practice, thymic carcinoma must be differentiated from carcinoma of other organs metastatic to or invading the anterior mediastinum, particularly carcinoma of the neighboring organs such as lung and malignant mesothelioma. Grossly, differentiated squamous cell carcinoma of the thymus is quite different from that of the lung. Thymic squamous carcinoma has much less of a tendency to become necrotic, but often becomes sclerotic in the central portion of the tumor. Histologically, a radial arrangement or palisading of the tumor cells at the borders of cell nests is not common in thymic carcinoma, and abrupt keratinization simulating Hassall corpuscles may be seen. Moderately prominent round nucleoli are found more frequently in thymic than in lung carcinoma. However, in poorly differentiated squamous cell carcinoma, mucoepidermoid carcinoma, small cell neuroendocrine carcinoma, clear cell carcinoma, and sarcomatoid carcinoma, distinction between thymic and lung carcinomas depends largely or entirely upon the location of the primary tumor and lymph node metastases. With regard to distinction of primary and metastatic carcinomas involving the thymus, CD5 immunohistochemistry is promising since, as already stated, carcinomas arising from other organs do not express CD5 (119). Analysis of larger numbers of tumors will be required to confirm the findings. CT evaluation and a history of smoking may also help in the diagnosis. Abnormalities in oncogenes and suppressor genes may be useful in the future.

Association of Epstein-Barr Virus with Development of Thymic Epithelial Tumors. Because of the presence in the thymus of undifferentiated carcinoma with features of lymphoepithelioma-like carcinoma, which is indistinguishable histologically from nasopharyngeal

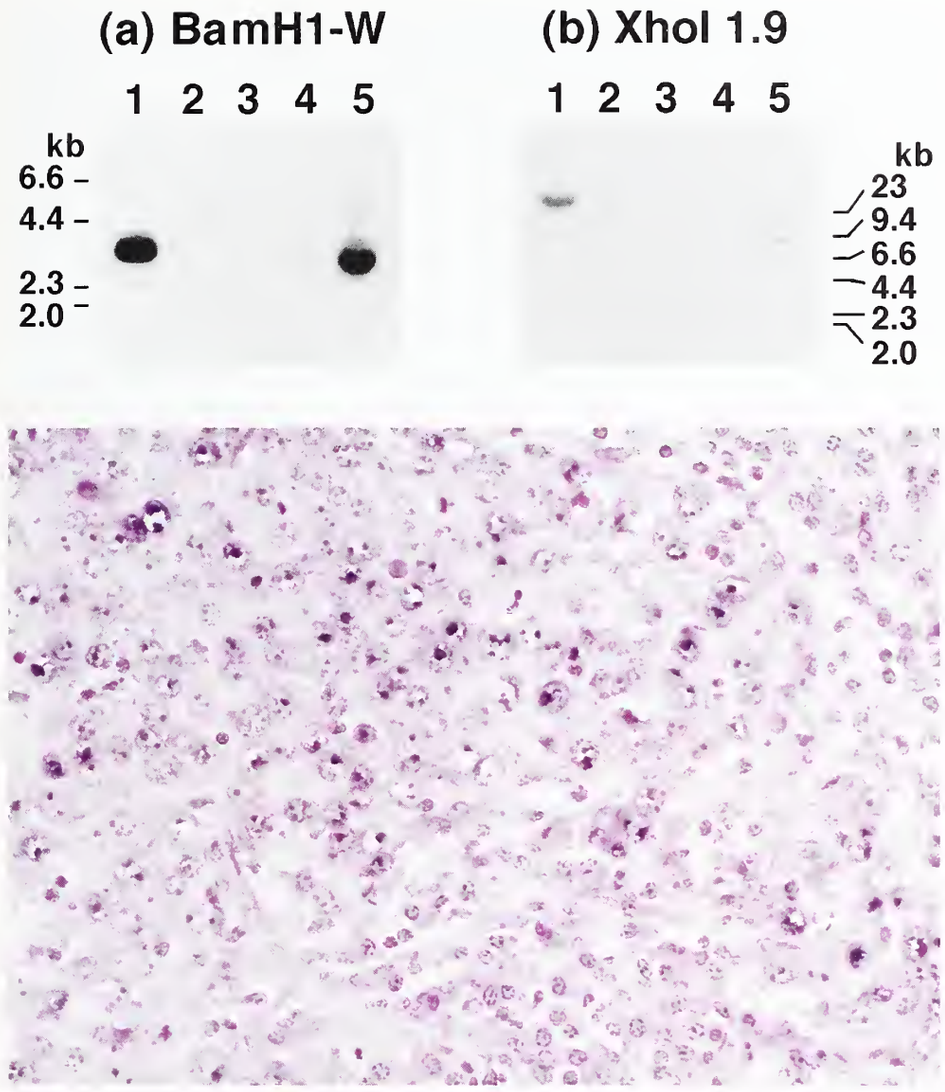


Figure 3-137
LYMPHOEPITHELIOMA-LIKE CARCINOMA WITH HOMOGENEOUS TERMINAL STRUCTURE OF EPSTEIN-BARR VIRUS (EBV) DNA AND POSITIVE IN SITU HYBRIDIZATION FOR EBER

Top: DNA extracted from cultured cell lines and fresh autopsy material from a "lymphoepithelioma-like" undifferentiated carcinoma was subjected to Southern blot hybridization after BamH1 digestion. As probes, 32P-labeled BamH1-W (detecting an internal repetitive sequence) and XhoI 1.9 (detecting a terminal repetitive sequence) fragments were used in (a) and (b), respectively. 1: Raji cell; 2: Ramos cell; 3, 4, and 5: tissues of spleen, liver, and liver metastasis from the autopsy case, respectively. (Fig. 3 from Matsuno Y, Mukai K, Uhara H, et al. Detection of Epstein-Barr virus DNA in a Japanese case of lymphoepithelioma-like thymic carcinoma. Jpn J Cancer Res 1992;83:127–30.)

Bottom: In situ hybridization on paraffin sections using an oligonucleotide probe for EBER reveals positive signals in a majority of tumor cells. No signals were seen in control sections treated with RNase (same case as that in figure 3-124).

undifferentiated carcinoma, an association with Epstein-Barr virus (EBV) has been suspected. The above-described tumor has been referred to previously by various names including lymphoepithelioma of the Schmincke and Regaud type, transitional carcinoma, squamous cell carcinoma, and undifferentiated carcinoma, although it is now understood to be a poorly differentiated form of squamous cell carcinoma since it contains desmosomes, tonofibrils, and cytokeratins.

Association of EBV with thymic lymphoepithelioma-like carcinoma was first reported by Leyvraz et al. in 1985 (129), who clarified the serologic profile: the presence of EBV-associated nuclear antigen in the carcinoma cells and a high level of the viral genome in the DNA, suggesting a role of EBV in the genesis of thymic carcinoma. In 1988, another case was reported by Dimery et al. (116), who stated that EBV was causally related to the development of thymic lymphoepithelioma-like undifferentiated carcinoma, since an EBV-hybridizing fragment was present in the tumor DNA genome but absent in the DNA of peripheral blood lymphocytes.

We investigated the association of EBV in 26 thymic epithelial tumors, including 8 noninvasive and 13 invasive thymomas and 5 thymic carcinomas (133). A homogeneous terminal structure of the viral DNA was determined in a single case of lymphoepithelioma-like thymic carcinoma, indicating clonal growth (fig. 3-137, top), whereas this was absent in thymoma or cancers of other histologic types. In addition, in situ hybridization for EBV-encoded small RNA (EBER) was positive in a majority of the lymphoepithelioma-like carcinoma cells (fig. 3-137, bottom). Lymphoepithelioma-like thymic carcinoma might represent a unique pathologic entity

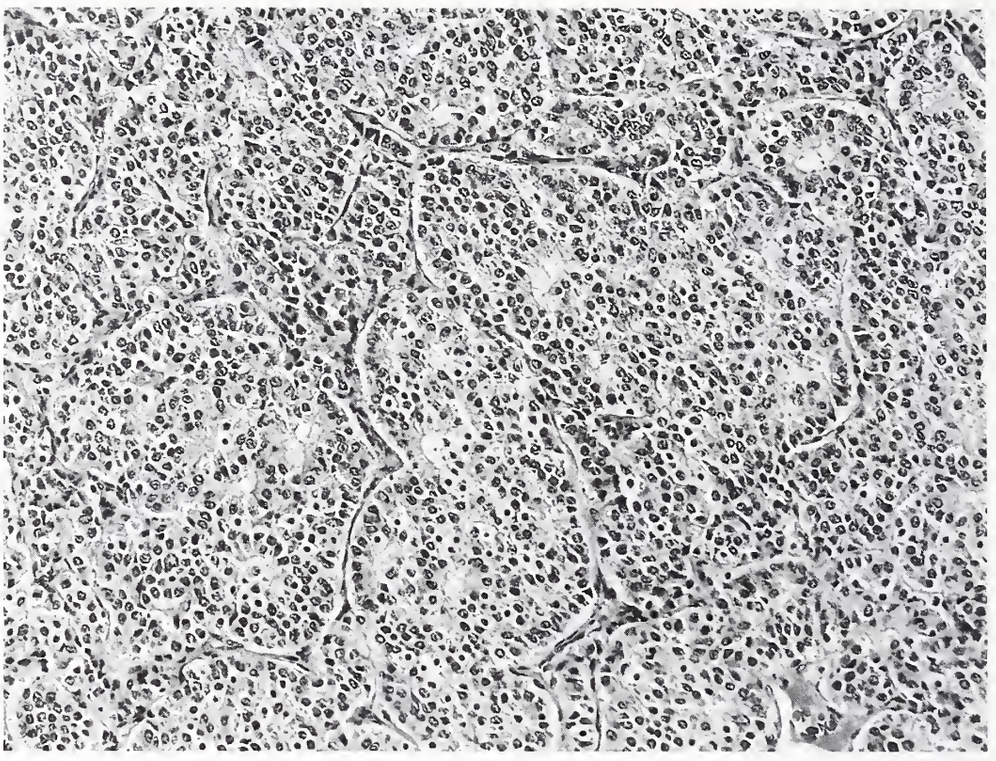


Figure 3-138
CARCINOID TUMOR
WITH ROSETTES

Medium-sized tumor nests are composed of polygonal to low columnar cells with oval bland nuclei and a small amount of cytoplasm, forming frequent rosettes. The stroma is made up of delicate blood vessels closely associated with tumor cells.

distinct from EBV-negative thymic epithelial tumors (133).

Weiss et al. (153) found that of 14 cases of extra-nasopharyngeal lymphoepithelioma (3 palatine tonsil, 1 oral floor, 1 pyriform sinus, 4 skin, 4 lung, and 1 uterine cervix), only 1 lung cancer showed a positive in situ hybridization signal for the EBV genome. They concluded that despite the histologic similarity, most lymphoepithelioma-like carcinomas probably have a pathogenesis different from that of nasopharyngeal lymphoepithelioma. However, no lymphoepithelioma-like thymic carcinomas were included in their series.

Although we did not find an association of EBV in 21 cases of thymoma, there is a report indicating that all of 3 thymomas and 3 of 5 thymic lymphoid hyperplasias in a Hong Kong study were positive for the EBV genome by Southern blot analysis using the BamH1-W fragment as the EBV-DNA probe (134). Such a high incidence of EBV association in thymic lesions may be due to the endemic nature of EBV in the studied area or a genetic predisposition of the population to EBV infection. However, the EBV-DNA detected could well have been present in the infiltrating lymphocytes and not in the epithelial cells, and therefore clonality of the positive cells must be confirmed in this study.

CARCINOID AND RELATED TUMORS

Carcinoid tumor of the thymus is another category of mediastinal tumor, which until 1972 was referred to by such terms as carcinoid tumor of the mediastinum, epithelial thymoma, mediastinal bronchial adenoma, parathyroid adenoma, and unclassified mediastinal tumor. Kay and Willson (164) described an ACTH-secreting thymoma in a patient with Cushing's syndrome in 1970, the histology and ultrastructure of which were typical of carcinoid tumor, but they refrained from labeling it "carcinoid." This was understandable, since most investigators at that time held the prevailing view that one should hesitate to make a diagnosis of carcinoid tumor unless it was of intestinal origin. In fact, even tumors of bronchial origin were classified as bronchial adenoma. In 1966, we saw one anterior mediastinal tumor with features typical of carcinoid tumor, with rosettes (fig. 3-138), but we did not report it as carcinoid tumor. When Rosai and Higa (170) reported eight anterior or anterosuperior mediastinal tumors in 1972 and reviewed eight other cases reported previously under various names, they considered such tumors to be endocrine neoplasms of thymic origin, which were "related to carcinoid tumors" of other organs, such as those of the gastrointestinal

tract, lung, gallbladder, bile duct, and pancreas. In a separate communication, Rosai et al. (171) also described three cases of "mediastinal endocrine neoplasm in patients with multiple endocrine adenomatosis," which were histologically identical to the eight cases described separately and were regarded as neoplasms belonging to the carcinoid tumor family. Although they did not designate these cases as carcinoid tumors of the thymus, these two reports were considered to represent the first documented categorization of carcinoid tumor of the thymus as a distinct entity. Thereafter, several reports appeared describing carcinoid tumors (161,166,176,179,180). However, the number of cases were insufficient to characterize the morphology and function of these tumors and distinguish them from carcinoid tumors of other organs.

Definition, Subtyping, and Related Tumors. Carcinoid tumor is a well-differentiated neuroendocrine tumor of low-grade malignancy. In the spectrum of neuroendocrine tumors, carcinoid tumor occupies one extreme end, and highly malignant, poorly differentiated small cell carcinoma occupies the opposite end. Between these two tumor entities, there are so-called atypical carcinoid tumors and large cell neuroendocrine carcinoma.

Criteria for subtyping neuroendocrine tumors vary among investigators, and no standardized definition is available at present. In the lung, we follow the definition of Arrigoni et al. (157) for atypical carcinoids, that is, the presence of foci of coagulation necrosis and increased mitotic activity, in addition to some nuclear atypia. However, most carcinoid tumors of the thymus do contain small necrotic foci in large solid nests and have some mitotic activity. Therefore, it can be said that many thymic carcinoid tumors are histologically similar to atypical carcinoid tumors of the bronchus, although the presence of necrosis may be due to the size of the tumor, which is usually much larger than carcinoid tumor of the bronchus. This observation is supported by the general feeling of pathologists that thymic carcinoid tumors are biologically somewhat more malignant than bronchial carcinoid tumors, whereas the opposite seems to be true for small cell carcinoma (179,181). In order to avoid confusion with the nomenclature used for tumors in other organs, it is better not to use the term "atypical carcinoid tumor" in the mediastinum, although the term "atypia" can be used to describe some carcinoid tumors with foci of increased cellular atypia, such as that seen in large cell carcinoma.

In this Fascicle, we define carcinoid tumor as a tumor with neuroendocrine features and a histology similar to that of the tumor of the same name occurring in other organs such as the gastrointestinal tract and bronchus, regardless of the frequency of mitotic figures and the presence of foci of coagulation necrosis. As a variant form, there is spindle cell carcinoid tumor. Apart from the small cell (neuroendocrine) carcinoma described in the previous chapter, tumors related to thymic carcinoid tumor include those composed largely of solid nests of relatively large cells with finely granular cytoplasm, arranged in a pattern suggestive of endocrine tumor, with a closely associated, well-developed, fine vasculature, but a less marked organoid arrangement of the tumor cells in comparison with carcinoid tumor. Some of these tumors resemble the poorly differentiated form of medullary carcinoma of the thyroid gland. This type of tumor can be classified as nonsmall cell or large cell (neuroendocrine) carcinoma, in contrast to small cell carcinoma, and has recently become a focus of interest for pulmonary pathologists because of the presence of such tumors in the lung (177). Figure 3-139 indicates the relationships existing among neuroendocrine tumors of the thymus.

Although the thymic tumors in patients with Cushing's syndrome reported by Wick et al. (179) were carcinoid tumors, there are cases of probable small cell carcinoma complicated by Cushing's syndrome, as well as spindle cell tumor, which could be called spindle cell carcinoid tumor with increased nuclear atypia and proliferative activity (172,174). Where to draw the line between carcinoid tumor and large or small cell neuroendocrine carcinoma is controversial, as is the distinction between large (or small) cell carcinoma and poorly differentiated squamous cell carcinoma or adenocarcinoma in the lung.

Histogenesis. Carcinoid tumors of the intestine and bronchi were thought to arise from neuroendocrine cells present in those organs, which were believed to be of neural crest (neuroectoderm) origin. This hypothesis was advocated in the 1960s and 1970s by Pearse et al. (168) and the tumors were called APUDomas

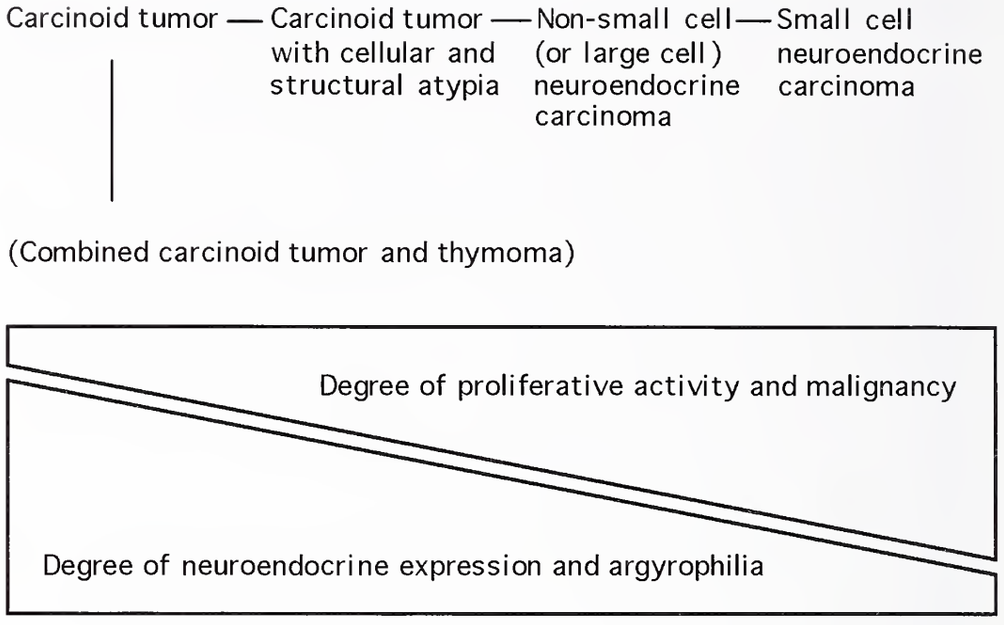


Figure 3-139
RELATIONSHIPS AMONG NEUROENDOCRINE TUMORS OF THE THYMUS

(amine precursor uptake and decarboxylation). Later, however, it was determined that neuroendocrine cells in the aerodigestive tract did not migrate from the neural crest, but came from the primitive epithelial cells originally present in those organs (169,173). This hypothesis can also be applied to carcinoid tumor of the thymus. Although argyrophil and argentaffin cells are present in chicken, pigeon, and reptile thymuses (160), and argyrophil cells (170) and immunoreactive calcitonin-containing cells may be found in human thymuses and are the presumed cells of origin of thymic neuroendocrine tumors, it is very difficult to prove the presence of Kulchitsky cells of the diffuse endocrine system in the human thymus. If in situ development and differentiation of neuroendocrine cells also occur in the human thymus, then the presence in the thymus of carcinoid tumor and small cell carcinoma with neuroendocrine features as well as the combined form of neuroendocrine and non-neuroendocrine tumors (described later) can be easily understood.

Incidence and Clinical Findings. In the cases reported by Rosai and Higa (170,171), all 16 patients (14 men, 2 women) were adults, with an age range of 21 to 66 years. None of the tumors were associated with signs of endocrine function including carcinoid syndrome and Cushing's syndrome. About one third of the patients were asymptomatic, and the tumors were found incidentally on chest roentgenograms. In the remaining patients, the nonspecific signs resulted from the anterior mediastinal mass, including chest pain, cough, and dyspnea. Three cases were associated with multiple endocrine adenomatosis: all three had chief cell hyperplasia with hyperparathyroidism; one had adenomatous hyperplasia of the pancreatic islets with Zollinger-Ellison syndrome; and one patient had suspected Zollinger-Ellison syndrome and chromophobe adenoma of the pituitary. In two of the patients, asymptomatic adenomatous hyperplasia of the adrenal cortex was detected.

The age range of the 15 patients (12 males, 3 females) collected by Wick et al. (179) from 1930 to 1980 was 15 to 67 years, with an average of 42 years. Six of their patients had associated ectopic adrenocorticotrophic hormone (ACTH) production, and 5 of these had Cushing's syndrome. Chest pain, cough, and dyspnea were present each in a few patients, and 5 patients were asymptomatic. None manifested carcinoid syndrome. One patient also had a parathyroid and islet cell tumor (multiple endocrine neoplasia [MEN] type 1), another developed islet cell carcinoma 11 years after resection of the thymic carcinoid tumor, and a third had a nonfunctional parathyroid adenoma at autopsy.

Birnberg et al. (159) reported two cases of thymic carcinoid tumor with hyperparathyroidism, one of which was complicated with parathyroid adenoma and the other with diffuse hyperplasia of

the parathyroid gland. The patient with parathyroid adenoma had a clear family history of MEN. Marchevsky and Dikman (166) described a case of mediastinal carcinoid tumor associated with parathyroid hyperplasia, medullary carcinoma of the thyroid, and adrenal neuroma, constituting incomplete Sipple's syndrome (MEA type II). These studies confirm that carcinoid tumor of the thymus is often a part of MEN and hyperplasia.

Valli et al. (178) reported eight cases of atypical carcinoid tumor of the thymus (6 males, 2 females; age range, 48 to 60). During the same 20-year period, there were 82 thymomas, 40 germ cell tumors, 26 cases of Hodgkin's disease, 15 B-cell sclerosing lymphomas, and 1 small cell carcinoma. There were no cases of typical carcinoid tumor. Tumor size was 7.5 to 10 cm and none showed evidence of an associated paraneoplastic neuroendocrine syndrome.

In our hospital, five cases of thymic carcinoid tumor were diagnosed in the last 31 years (1962 to 1993), and eight more consultation cases were analyzed. The patients ranged from 34 to 71 years of age, with an average of 56.1 years. Eight patients were male and five were female. Only two tumors functioned endocrinologically. Details of bioactive substances produced by the tumor are given in the section on immunohistochemistry.

In cases of carcinoid tumor of the lung, carcinoid syndrome hardly ever occurs unless there is metastasis to distant organs, such as the liver. However, we are not aware of any case of mediastinal carcinoid tumor associated with carcinoid syndrome, even among those with hematogenous metastases.

Nonfunctional thymic carcinoid tumors, such as those not associated with Cushing's syndrome, are often large and easily detected by routine chest X ray. They present as a large, radiopaque, noncystic anterior mediastinal mass projecting into the pleural space unilaterally or bilaterally (fig. 3-140). Fine calcifications may be present in the mass. On the other hand, thymic carcinoid tumors associated with Cushing's syndrome may be so small that they are undetectable by routine posterior-anterior and lateral chest roentgenograms. In such cases, CT is useful. Among five cases associated with Cushing's syndrome reported by Wick et al. (179), only one tumor was identified on routine chest X ray, two were found at autopsy, and two by CT. Of the total 15 cases, 5 showed osteoblastic bone metastasis, which was disclosed by skeletal survey roentgenograms and radionuclide bone scans.

Gross Findings. Functional carcinoid tumors may be as small as 1.3 cm (179), but nonfunctional tumors are often large when detected, encapsulated or circumscribed, with pale tan to gray-white, solid cut surfaces with or without scattered pinhead-sized areas of necrosis (figs. 3-141, 3-142). Irregular areas of coagulation necrosis or hemorrhage may also be present. The tumor frequently adheres to and at times invades surrounding organs or tissue such as the pleura, pericardium, lung, and adventitia of the major vessels. Fibrous bands, which are often seen in thymoma, are not present. Two independent tumors within a single thymus have been described in two instances. However, the possibility of a metastatic lesion should always be kept in mind, since lymph node metastasis is not rare.

Microscopic Findings. Classic carcinoid tumors are made up of solid nests, rosettes, and festoons of small to medium-sized, uniform polygonal cells, and less frequently, spindle cells; central round to oval finely granular nuclei with stippled chromatin; thin nuclear membranes; inconspicuous or small nucleoli; and a minimal to moderate amount of lightly eosinophilic, very finely granular cytoplasm (fig. 3-143). The stroma is scanty and delicately vascular. Mitotic figures are few to moderate in number (2 to 21 per 1.52 mm^2 [10 high-power fields]) (fig. 3-144) (178). Central coagulation necrosis is often found within large cell nests (fig. 3-143D). Foci of coagulation necrosis and mitotic activity are features of "atypical carcinoid" of the bronchus according to Arrigoni et al. (157). However, it is better not to use the term "atypical" in the mediastinum, unless typical carcinoid tumor is combined with areas showing features of poorly differentiated or undifferentiated carcinoma.

Wick et al. (179) described four additional histologic patterns in thymic carcinoid tumors: 1) a very sclerotic fibrous stroma, compressing the tumor cell clusters, and occasionally producing an "Indian file" arrangement; 2) a cribriform pattern; 3) sheet-like masses of tumor cells with a scanty vascular stroma showing only a vaguely organoid cellular arrangement; and 4) the classic carcinoid tumor pattern, but with focal collections of intracellular brown-gray granular pigments, which are

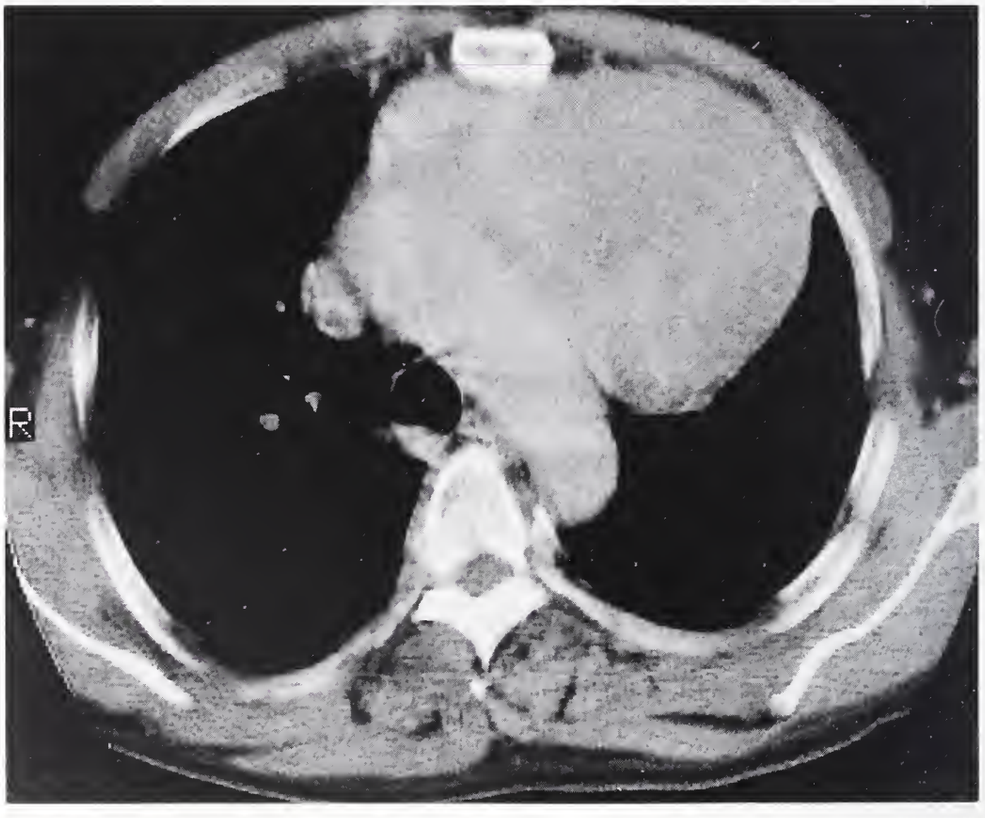


Figure 3-140
CARCINOID TUMOR
WITH CELLULAR ATYPIA

Top: Posterior-anterior chest roentgenogram reveals a large tumorous density overlapping the left pulmonary hilus and the convexity toward the left lung. The contents of the mediastinum are displaced toward the right lung. There is pleural thickening on the left.

Bottom: CT at the level of the aortic arch discloses a clearly defined tumorous density, which displaces the superior vena cava and ascending aorta to the right and compresses the lungs bilaterally. (Figures 3-140 and 3-141 are from the same case.)

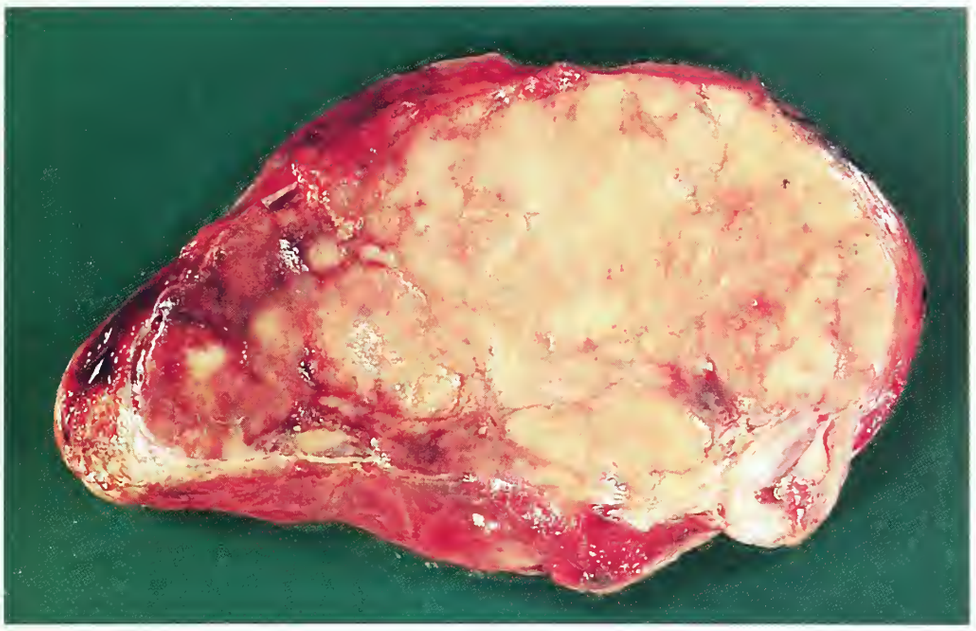


Figure 3-141
CARCINOID TUMOR

Horizonal section of the tumor reveals encapsulation with thin fibrous tissue and a granular to faintly lobulated yellowish tan medullary cut surface with no recognizable areas of necrosis.

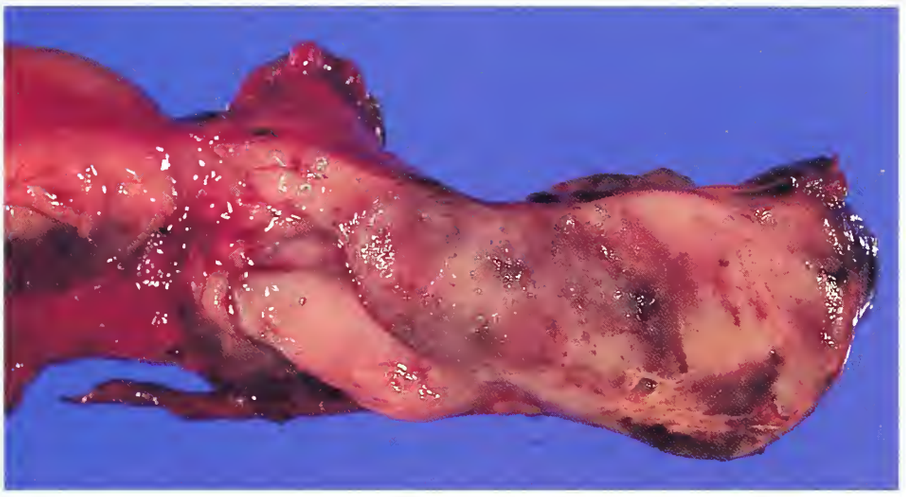


Figure 3-142
CARCINOID TUMOR

Left: Posterior aspect of a surgically resected thymus with tumors in the right lobe. The membranous tissue with a smooth surface attached to the right lobe is a portion of the pericardium.

Above: Horizontal section of the thymus reveals a thinly encapsulated tumor with a pale tan congested surface showing yellow streaks of necrosis. Three smaller tumors were present in the same lobe, and multiple lymph nodes with metastases in the mediastinum and neck were removed at the same time. (Figures 142 and 143 are from the same case.)

PAS positive and appear to be lipofuscin (figs. 3-145–3-147). In the cases we examined, however, the sclerotic stroma did not compress the tumor cell nests, and a tumor with a vaguely organoid pattern showed a typical organoid pattern in other areas. A sclerotic stroma and lipofuscin-like intracellular pigments indicate a longstanding tumor, and a cribriform pattern probably indicates the presence of small foci of liquefaction necrosis within the cell nests. A vaguely organoid pattern may simply indicate a lesser degree of differentiation and greater proliferative activity of the tumor cells. We saw a case with cervical lymph node metastasis which

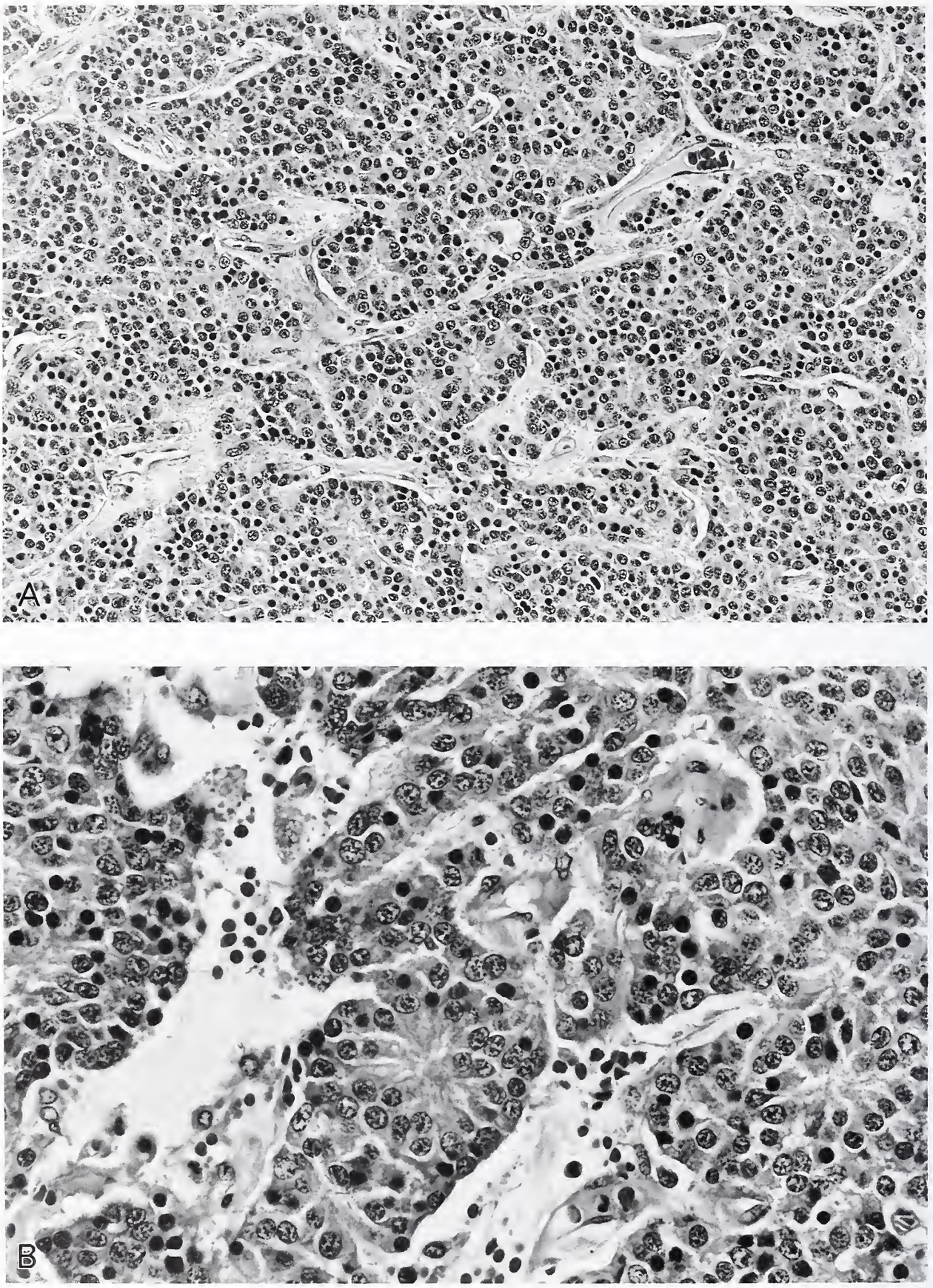


Figure 3-143
CARCINOID TUMOR

A,B: Irregularly shaped nests of tumor cells with round to oval bland nuclei, inconspicuous nucleoli, and finely granular cytoplasm are closely associated with delicate blood vessels. Rosettes are frequently evident.

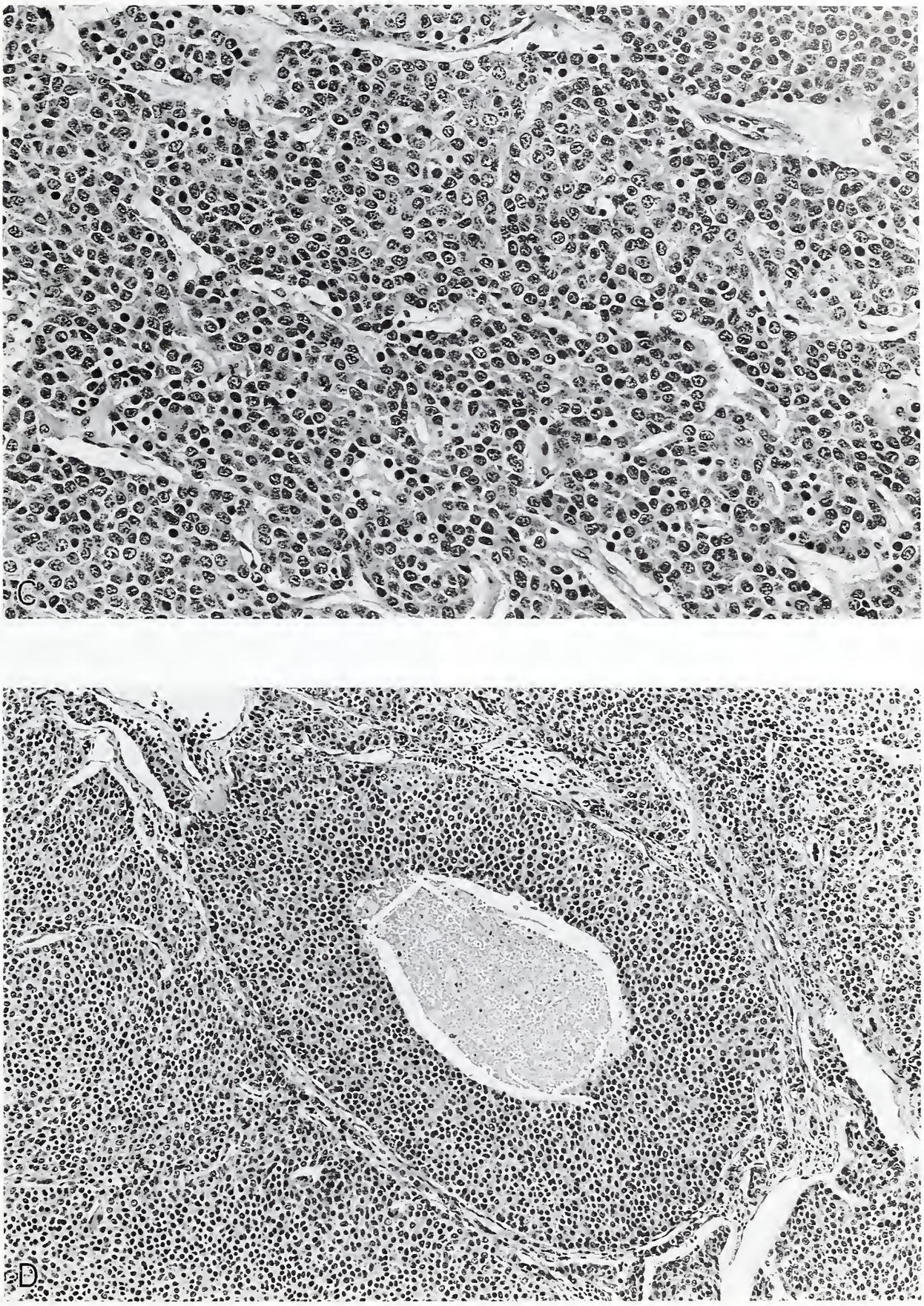


Figure 3-143 (Continued)
C: Metastasis in lymph nodes is composed of slightly larger cells with a few mitotic figures, without rosette formation.
D: A focus of coagulation necrosis is seen in the center of a tumor nest.

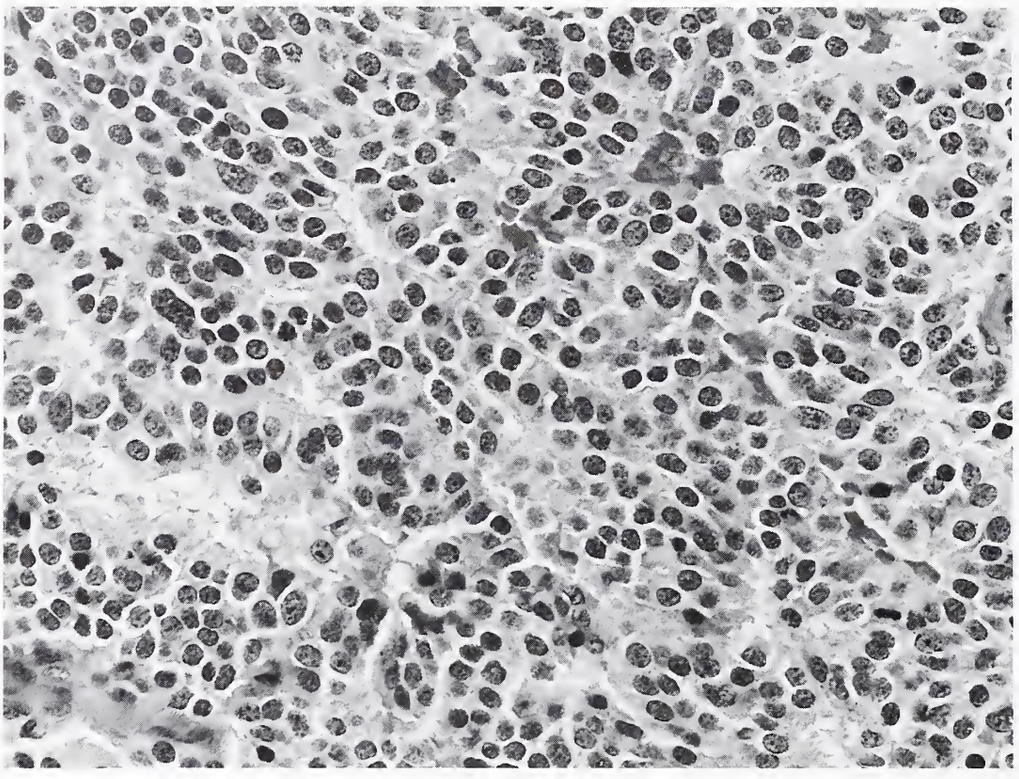


Figure 3-144
CARCINOID TUMORS WITH MITOTIC FIGURES

At least two mitotic figures, one at the left upper and another at the right lower portion of the figure, are evident in this high-power view of an area with histologic features typical of carcinoid tumor.

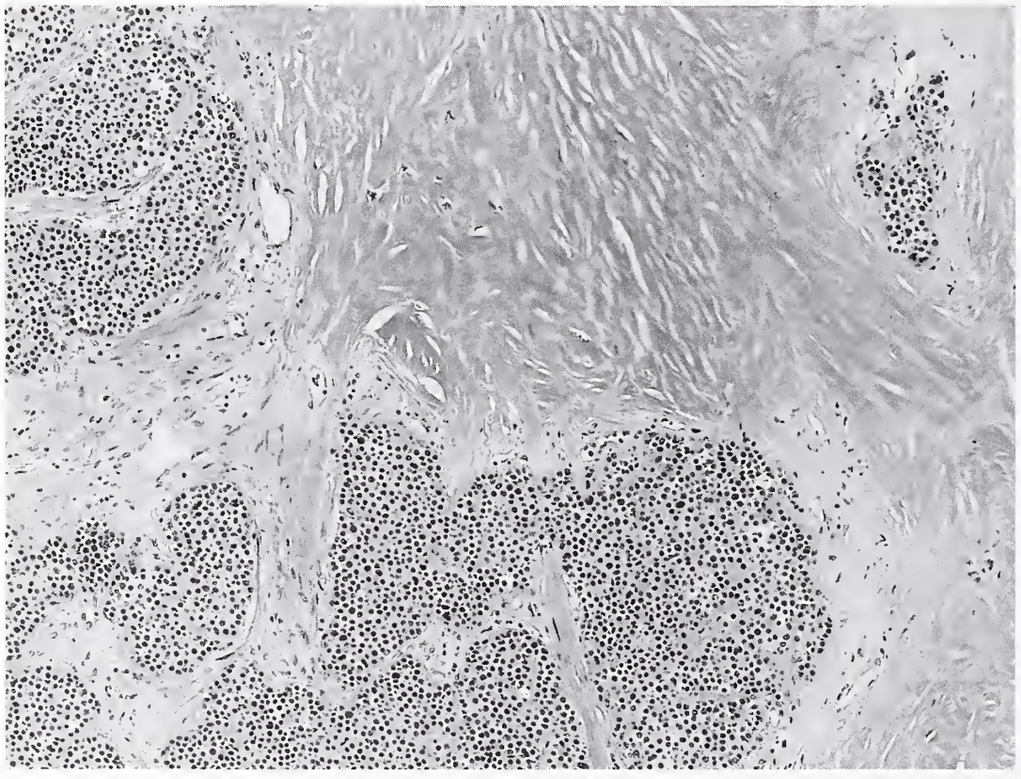


Figure 3-145
CARCINOID TUMOR WITH SCLEROTIC STROMA

Marked sclerosis and hyalinization of the stroma is evident. Tumor cells at the right upper corner appear to be undergoing atrophy due probably to an impaired blood supply.

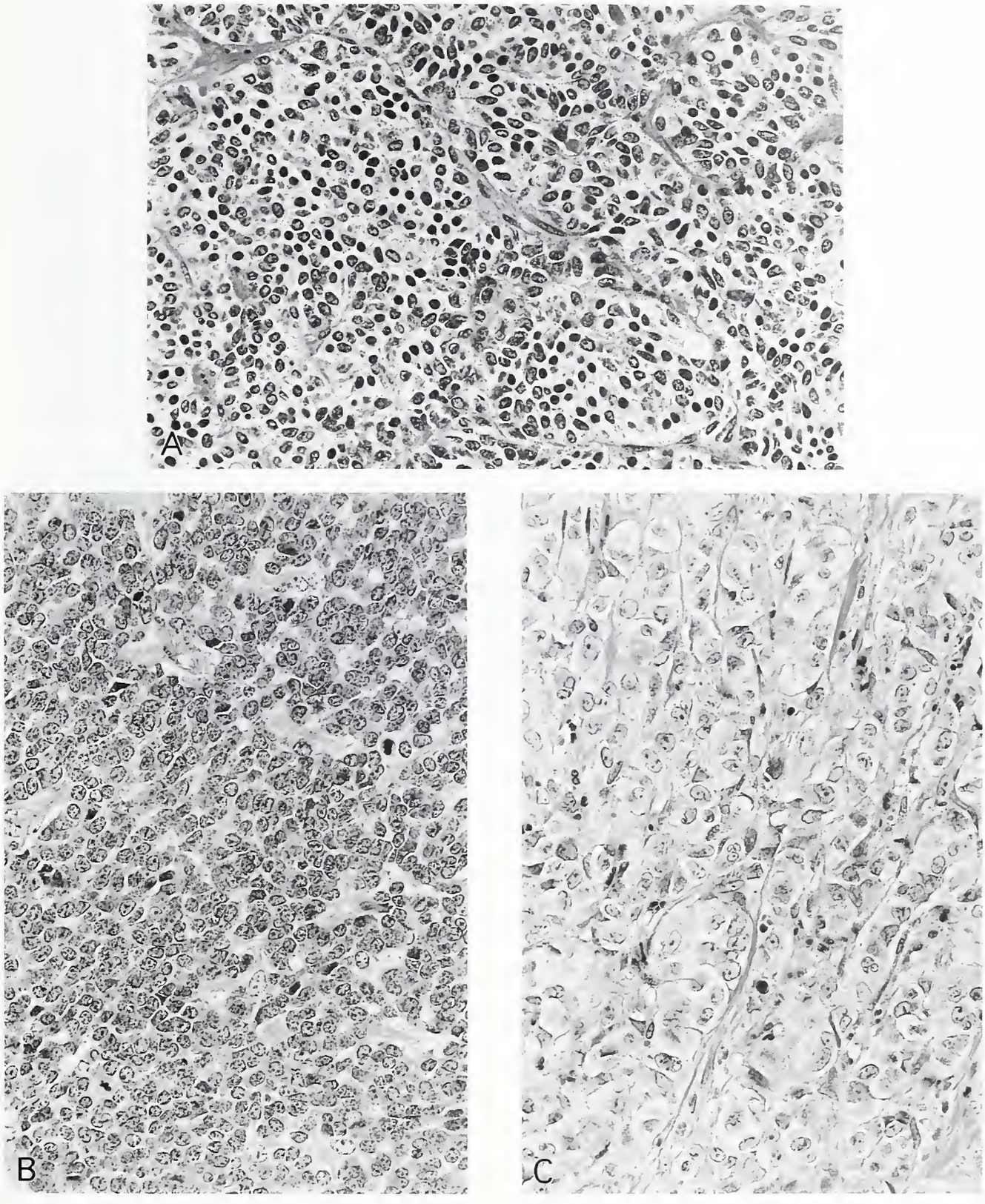


Figure 3-146
CARCINOID TUMOR WITH CELLULAR AND STRUCTURAL ATYPIA

A: In the primary tumor, polygonal to oval tumor cells tend to form rosettes and are associated closely with blood vessels, features characteristic of carcinoid tumor.

B: In other areas, larger tumor cells with an increased nuclear to cytoplasmic ratio and an increased number of mitotic figures grow diffusely, as in undifferentiated carcinoma.

C: A recurrent tumor in a lymph node, which was found 12 years later, shows a further increase in cellular atypia. (Courtesy of Dr. Tadakazu Shimoda, Tokyo.)

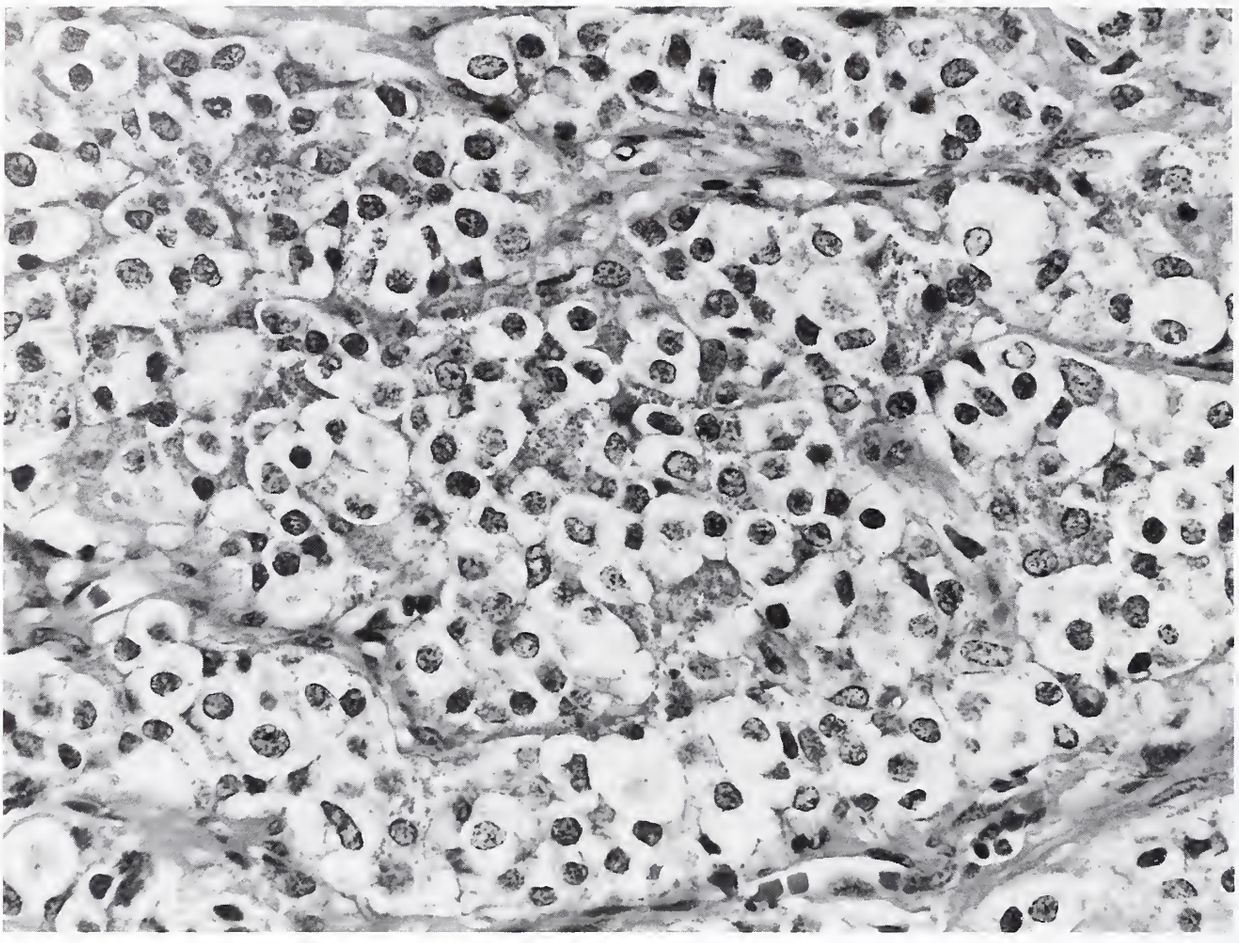


Figure 3-147
CARCINOID TUMOR WITH LIPOFUSCIN-LIKE PIGMENT
The tumor cells possess ballooned, clear cytoplasm, which contains coarsely granular brown pigment.

was similar to medullary carcinoma of the thyroid (fig. 3-146C). However, the primary tumor in the mediastinum removed 12 years earlier was composed in part of a typical carcinoid tumor (fig. 3-146A) and in part of poorly differentiated tumor with a less organoid arrangement (fig. 3-146B). The presence of features typical of carcinoid tumor led us to classify the tumor not as large cell neuroendocrine carcinoma but as carcinoid tumor with foci of increased cellular and structural atypia. The sustentacular cell (158) is considered to be an organoid arrangement marker, but it is identified only infrequently in thymic carcinoid tumors (fig. 3-148).

Spindle-shaped tumor cells were considered to be a component of classic thymic carcinoid tumor by Wick et al. (fig. 3-149) (180). If the entire tumor is composed of spindle cells, as in a spindle cell carcinoid tumor of the lung periphery, it should be designated *spindle cell carcinoid tumor* (fig. 3-150); this tumor can cause diagnostic difficulty. Glandular structures, which could well be rosettes with exaggerated lumina, may be seen (fig. 3-149D), but the presence of mucus-producing cells has not been described in thymic carcinoid tumors. Carcinoid tumor with glandular structures is of interest in view of the presence of small cell neuroendocrine carcinoma with glandular structures (fig. 3-131). Although rare, there may be abundant extracellular connective tissue mucin in the stroma, giving an appearance of mucinous carcinoid tumor, but there is no cytoplasmic mucus (fig. 3-151).

The argentaffin reaction is negative in thymic carcinoid tumor, as in bronchial carcinoid tumor. The argyrophil reaction is variably positive (figs. 3-152, 3-153).

Carcinoid tumor containing non-neoplastic melanocytes and melanophages was reported by Ho and Ho (162). Melanocytes were also found in thymoma (see fig. 3-74).

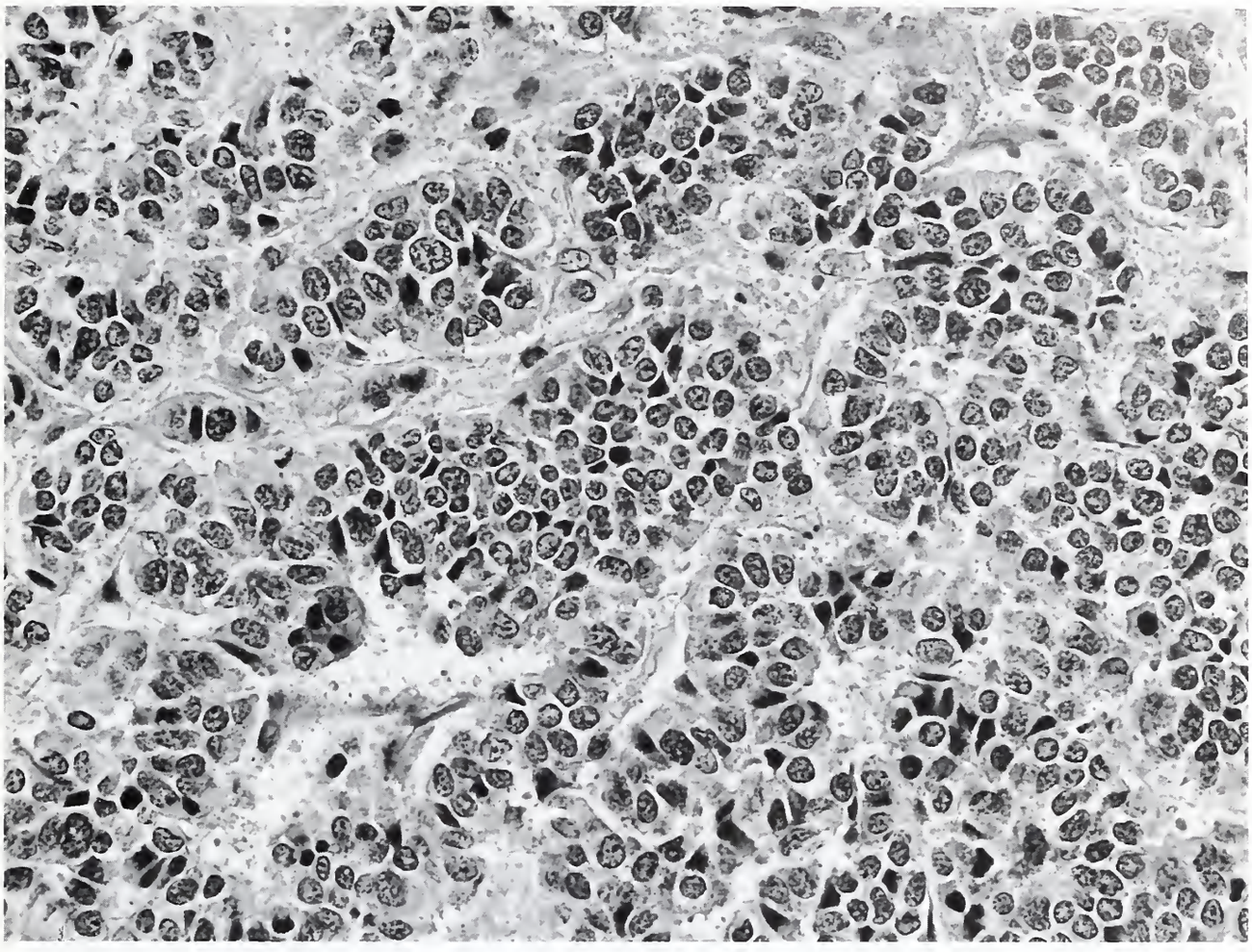


Figure 3-148
CARCINOID TUMOR WITH SUSTENTACULAR CELLS

Solid tumor cell nests are bordered in some areas with spindle or stellate cells, which were S-100 protein positive immunohistochemically (see also figure 3-164).

Electron Microscopic Findings. Centrally located nuclei contain evenly dispersed chromatin and inconspicuous nucleoli in most cases. The cytoplasm contains variable numbers of mitochondria and Golgi apparatuses. The rough endoplasmic reticulum is often abundant in many cases, and there is a moderate amount of smooth endoplasmic reticulum in some cases, particularly those complicated by Cushing's syndrome. Membrane-bound dense-core granules 150 to 500 nm in diameter, which are of the neurosecretory type, are always present and abundant in most thymic carcinoid tumors (fig. 3-154). Cellular attachments of the desmosomal type may be present, but are often poorly developed. Cytoplasmic fibrils, probably intermediate filaments, may be arranged in whorls, usually in Golgi areas. A basal lamina can be identified, although it is scanty (180).

Immunohistochemical Findings. As in carcinoid tumors at other locations, the tumor cells of thymic carcinoid tumor immunostain for neuron-specific enolase (NSE), chromogranin A, synaptophysin, and neural cell adhesion molecule (N-CAM) with variable intensity (figs. 3-155–3-158). Serotonin has been demonstrated focally in a few cases, including one in the series of Wick et al. (180), but gastrin-releasing peptide (GRP) has not. Somatostatin was frequently detected (7 of 12 cases) in Wick's series, and in two of three cases we examined (fig. 3-159). Study of five tumors by Herbst et al. (161) revealed the presence of NSE in 2, chromogranin A in 2, ACTH in 2, calcitonin in 1, neurotensin in 3, and cholecystokinin in all 5. In all five cases, more than two hormones were detected immunohistochemically; however, calcitonin gene-related peptide,

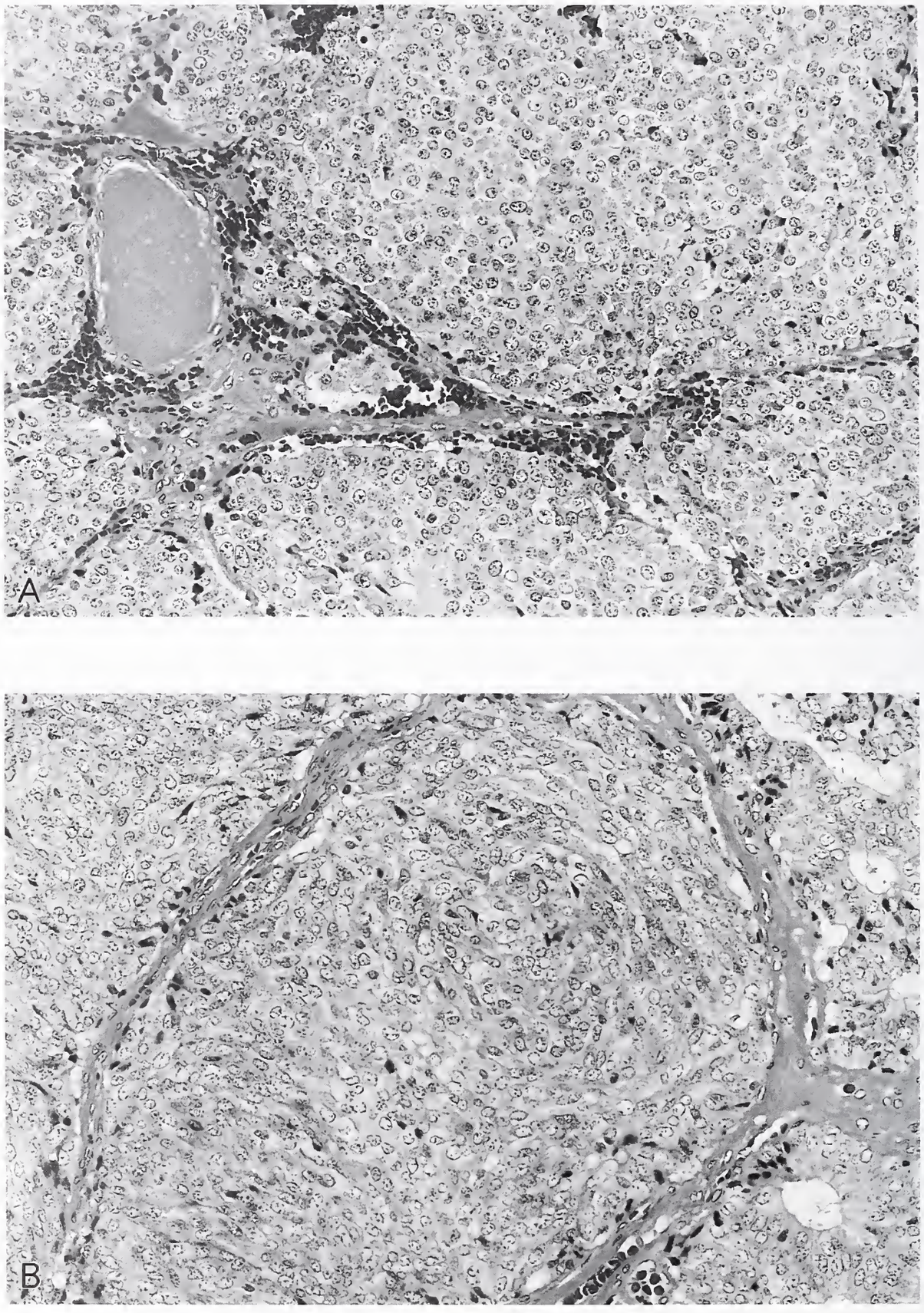


Figure 3-149

CARCINOID TUMOR WITH SPINDLE CELLS AND GLANDULAR STRUCTURES

A: Large solid nests are composed of round to polygonal cells with vesicular nuclei, small nucleoli, and a small amount of cytoplasm, which could be diagnosed as carcinoid tumor with cellular atypia.

B: In other areas cell nests consist of spindle cells arranged in whorls, which are adjacent to areas with glandular structures.

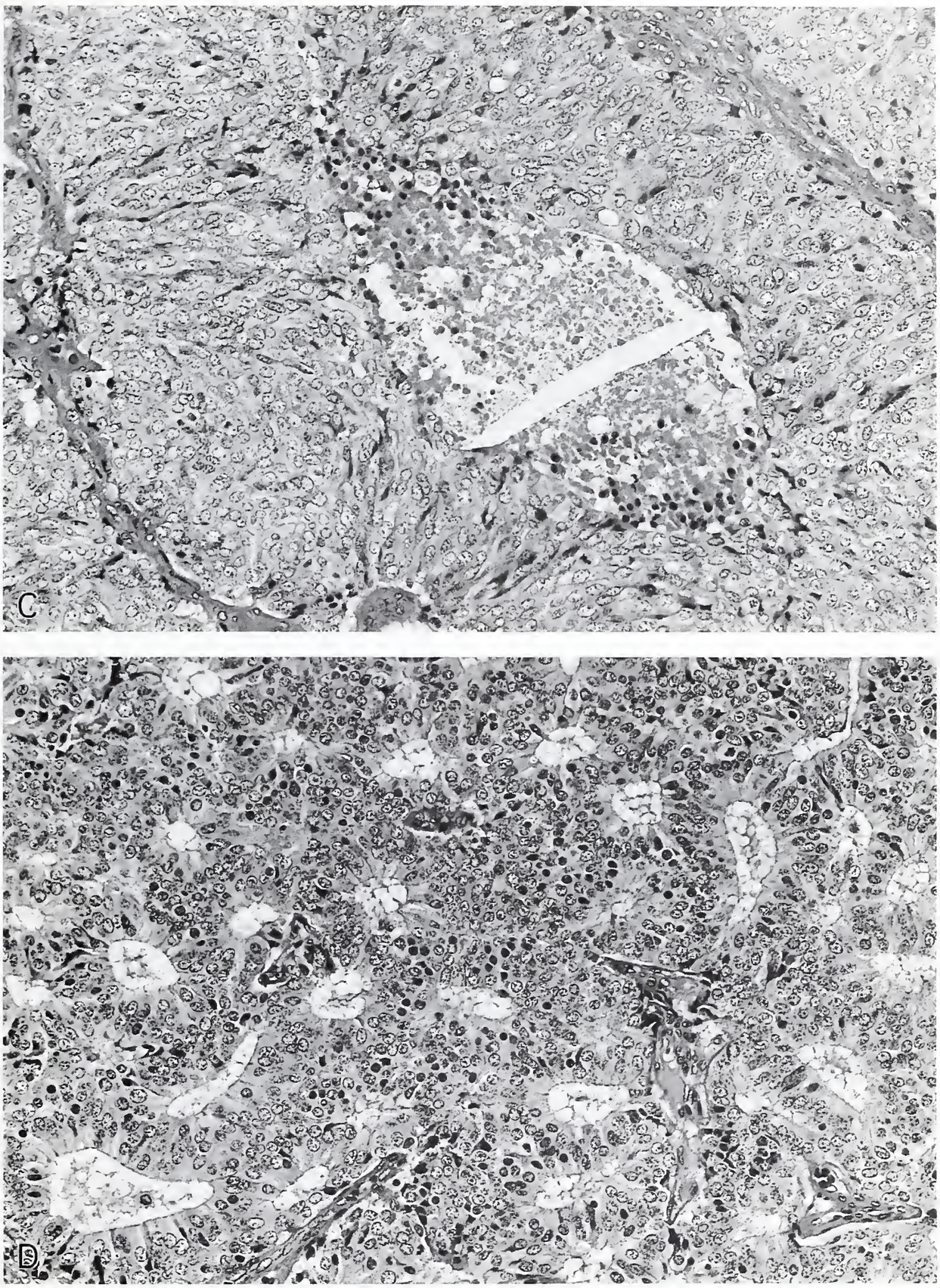


Figure 3-149 (Continued)

C: Central necrosis is seen in a large tumor nest made up of spindle cells.

D: Many well-defined glandular structures are present in other areas. This tumor was immunohistochemically positive for chromogranin A, somatostatin, and alpha-hCG. Grimelius stain was also positive, but alcian blue-PAS was negative (same case as that in figures 3-140, 3-141).

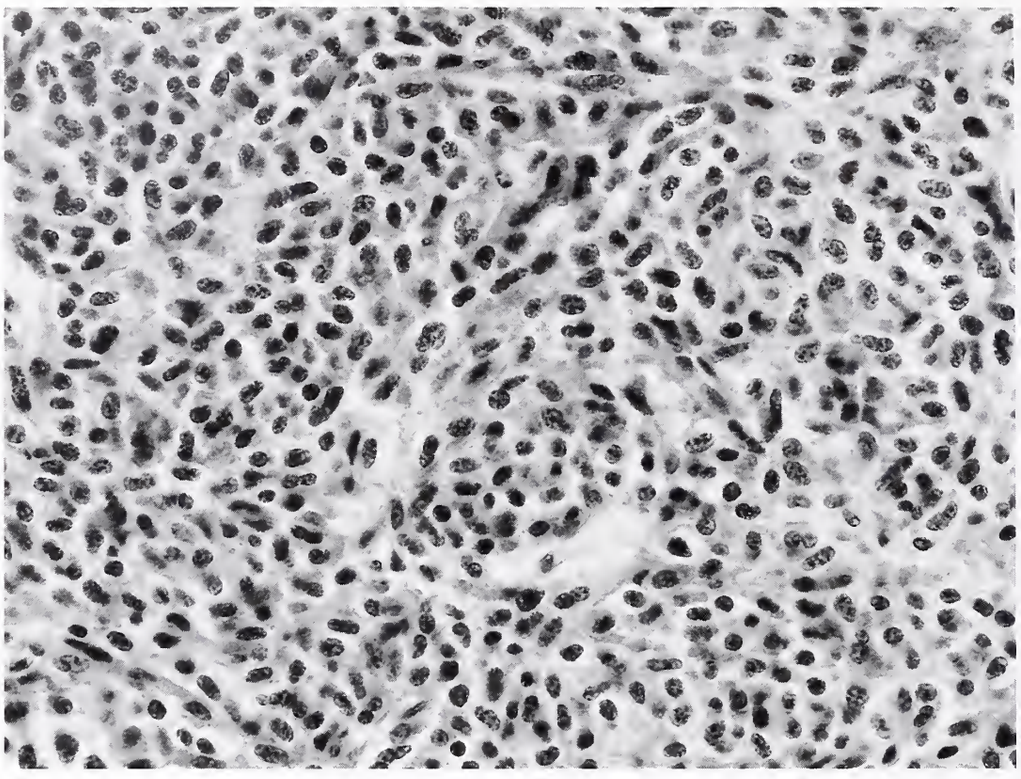


Figure 3-150
SPINDLE CELL CARCINOID TUMOR

The tumor shows diffuse growth and contains ill-defined nests of short spindle cells with oval finely granular nuclei, inconspicuous nucleoli, and finely granular cytoplasm. (Courtesy of Dr. Tetsuro Kodama, Kashiwa, Japan.)

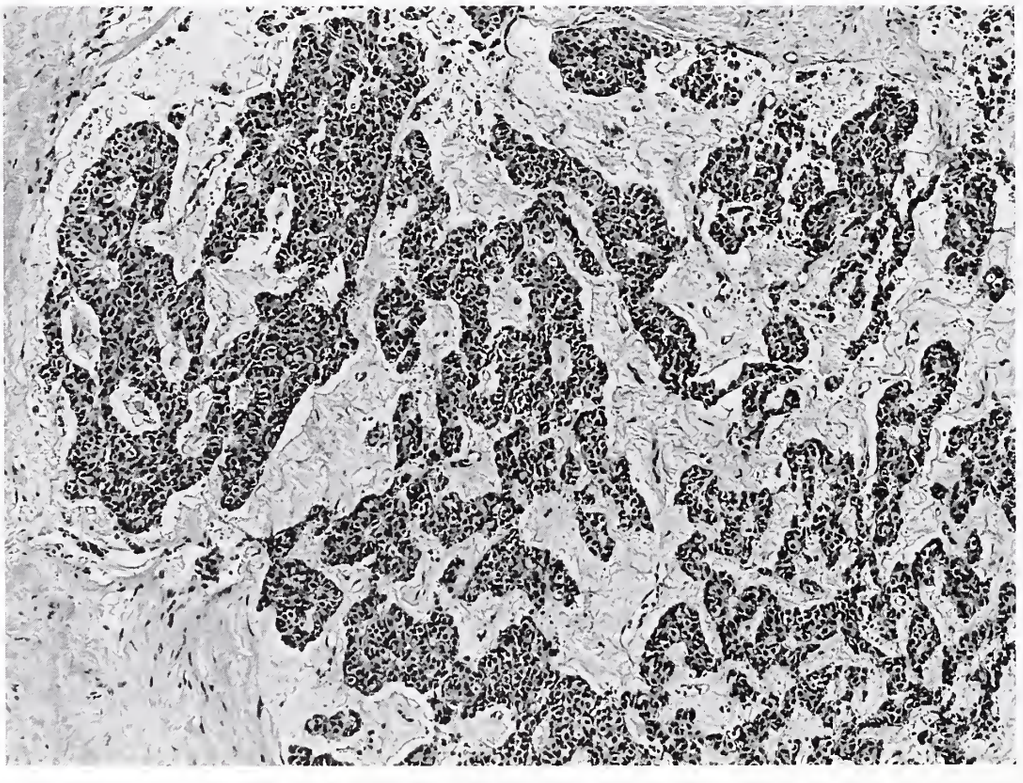


Figure 3-151
CARCINOID TUMOR WITH MUCINOUS STROMA

Abundant extracellular connective tissue type mucin is present in the stroma, giving a false impression of mucinous carcinoid tumor.

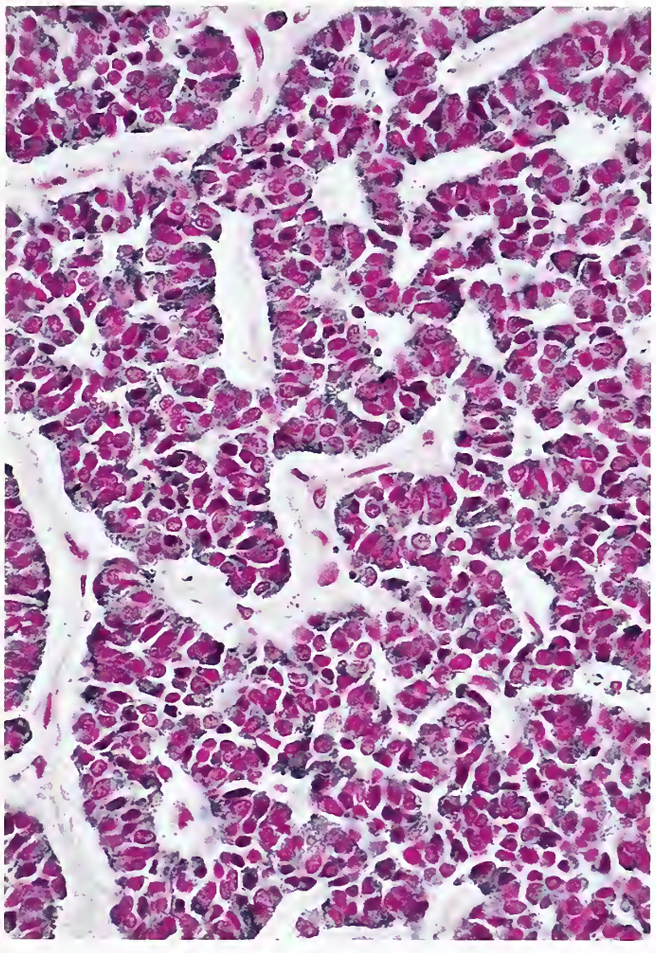


Figure 3-152
CARCINOID TUMOR WITH ARGYROPHILIA
Tumor cells in trabeculae or festoons show marked argyrophilia.

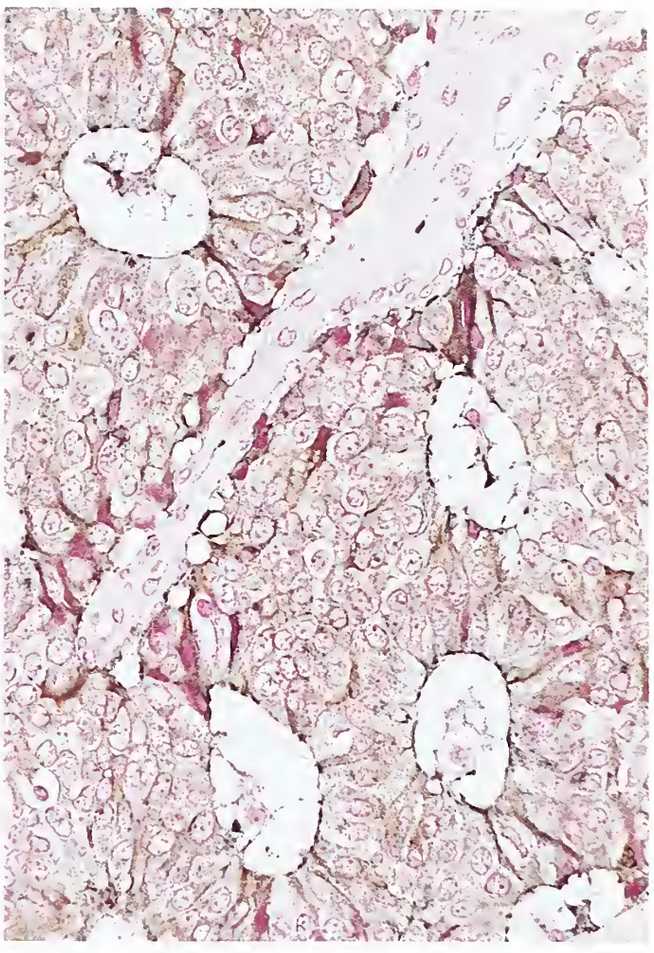


Figure 3-153
CARCINOID TUMOR WITH ARGYROPHILIA
Tumor cells arranged in glandular structures are frequently positive for Grimelius stain (same case as that in figure 3-149).

gastrin, somatostatin, substance P, and serotonin were not demonstrated in any. In eight atypical carcinoid tumors reported by Valli et al. (178), all were positive for cytokeratin, NSE, synaptophysin, and chromogranin; five cases were positive for calcitonin.

The most frequent paraneoplastic syndrome associated with thymic carcinoid tumor is Cushing's syndrome. Although four tumors tested at the Mayo Clinic showed the presence of intracytoplasmic immunoreactive ACTH, and three of them were associated with Cushing's syndrome clinically, it may be difficult to reveal the presence of ACTH immunohistochemically. In such cases, radioimmunoassay of an extract of tumor tissue confirms the presence of the peptide. In a case of carcinoid tumor with associated Cushing's syndrome reported by Huntrakoon et al. (163), the corticotropin-positive granules were present only in a few tumor cells. This finding was explained by either prompt secretion of the product or the presence of only a few cells capable of production. A 56-year-old male with a thymic carcinoid with cellular atypia which produced ACTH underwent surgical resection of the anterior mediastinal tumor (fig. 3-160). Pulmonary metastasis was found 18 months after surgery. He then developed hypernatremia and hypokalemia, and his blood ACTH and cortisol levels were elevated (419.8 pg/ml and 60 μg/dl, respectively). The tumor did not respond to cisplatin, adriamycin, vincristine, and cyclophosphamide therapy, and he died of metastases to the lung, heart, liver, kidney, pituitary gland, muscle, and bone. The tumor tissue at autopsy contained 26,000 pg/g ACTH. However, ACTH could not be demonstrated immunohistochemically in the surgically resected primary tumor or

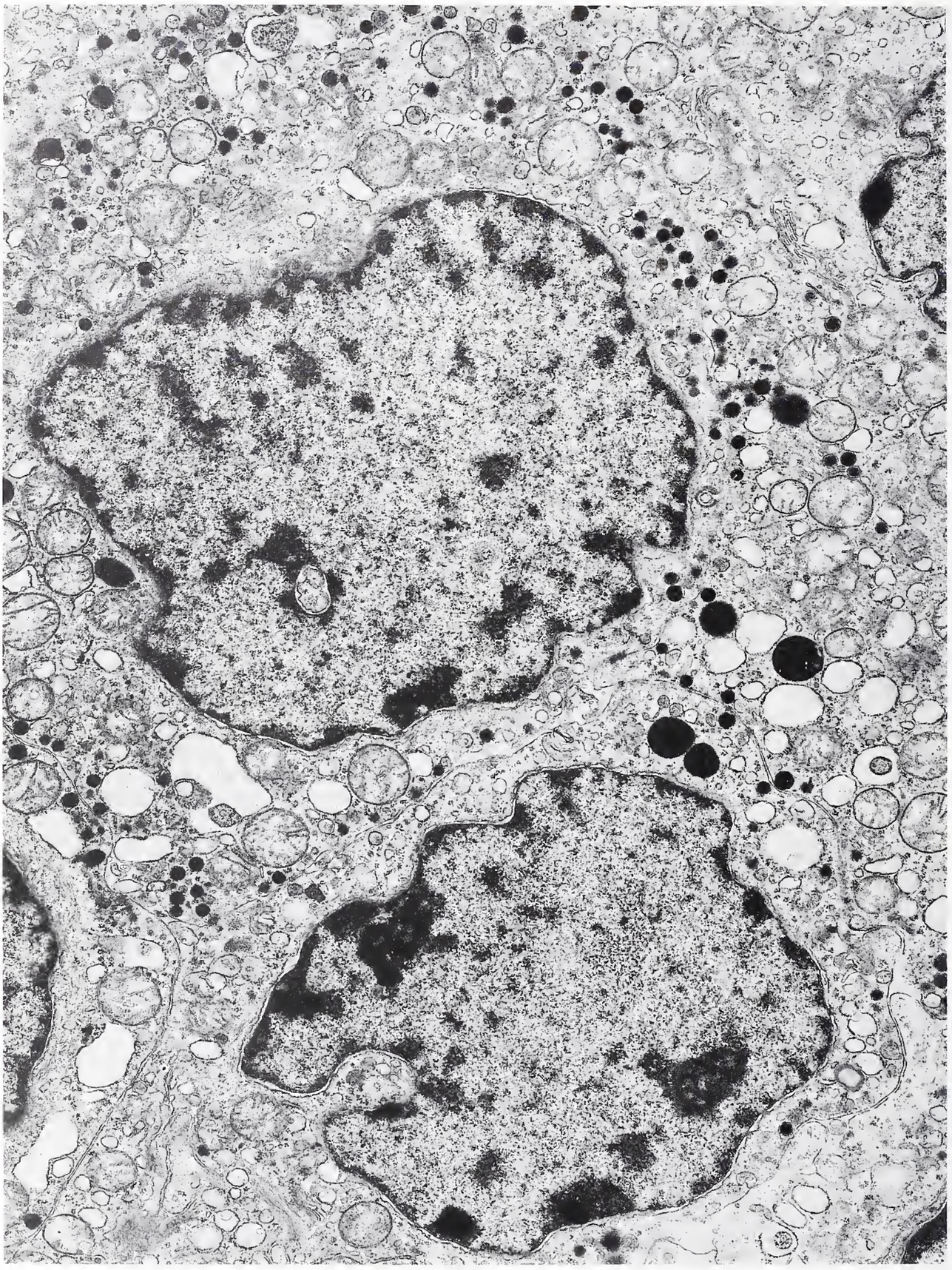


Figure 3-154
ULTRASTRUCTURE OF CARCINOID TUMOR WITH ECTOPIC ACTH PRODUCTION

Many neurosecretory type granules of about 160 nm in diameter are evident in cytoplasm of tumor cells. Mitochondria and smooth endoplasmic reticulum are moderately developed. The patient developed Cushing's syndrome, and laboratory data indicated ectopic production of ACTH (X12.000). (Courtesy of Dr. Toru Kameya, Sagamihara, Japan.)

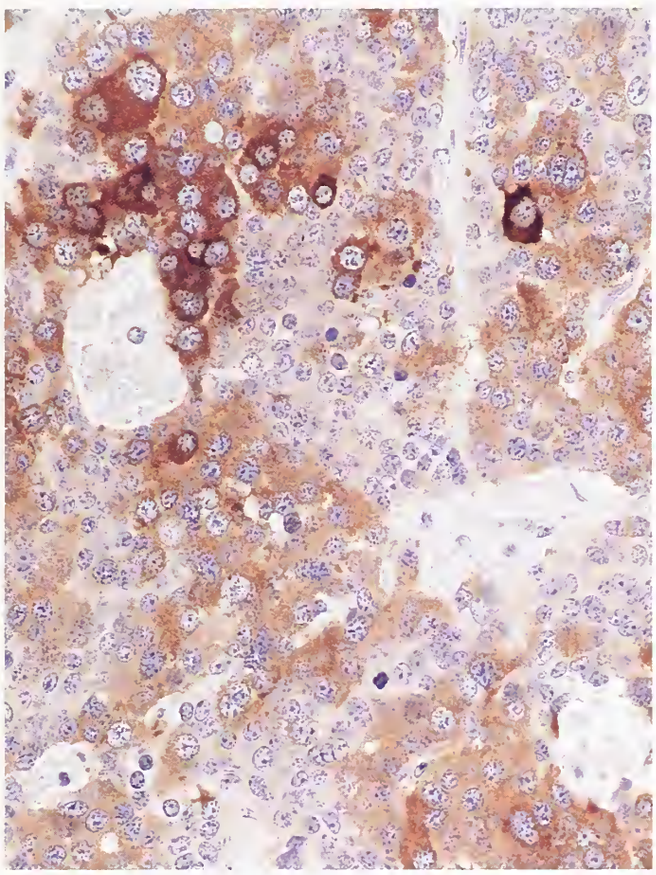


Figure 3-155
CARCINOID TUMOR WITH
IMMUNOREACTIVE NEURON-SPECIFIC ENOLASE

The tumor cells show various degrees of cytoplasmic staining for neuron-specific enolase (same case as that in figure 3-143).

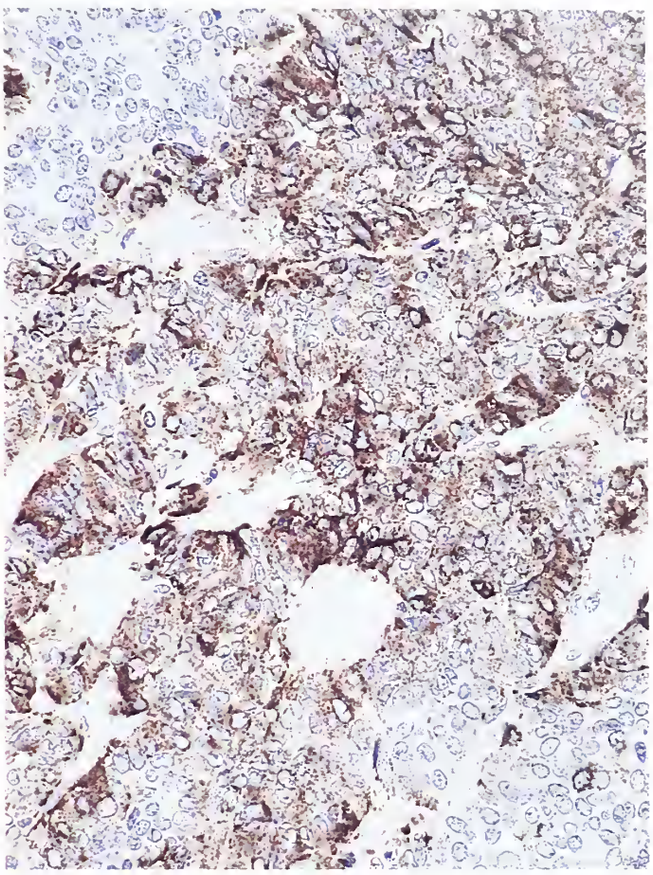


Figure 3-156
CARCINOID TUMOR WITH
IMMUNOREACTIVE CHROMOGRANIN A

Many tumor cells contain immunoreactive chromogranin A (same case as that in figure 3-146).

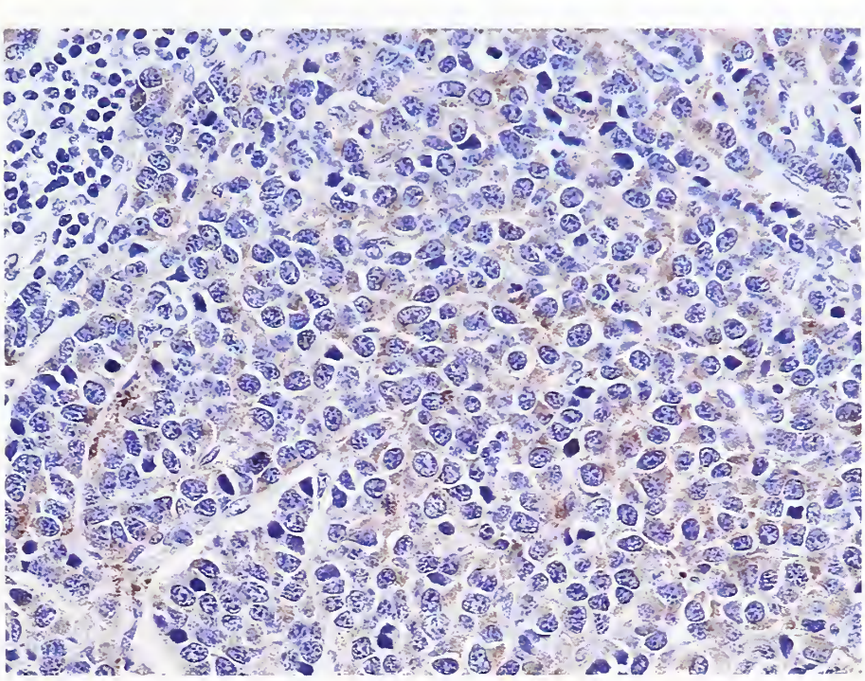


Figure 3-157
CARCINOID TUMOR WITH
IMMUNOREACTIVE SYNAPTOPHYSIN

The cytoplasm of the tumor cells is variably stained for synaptophysin.

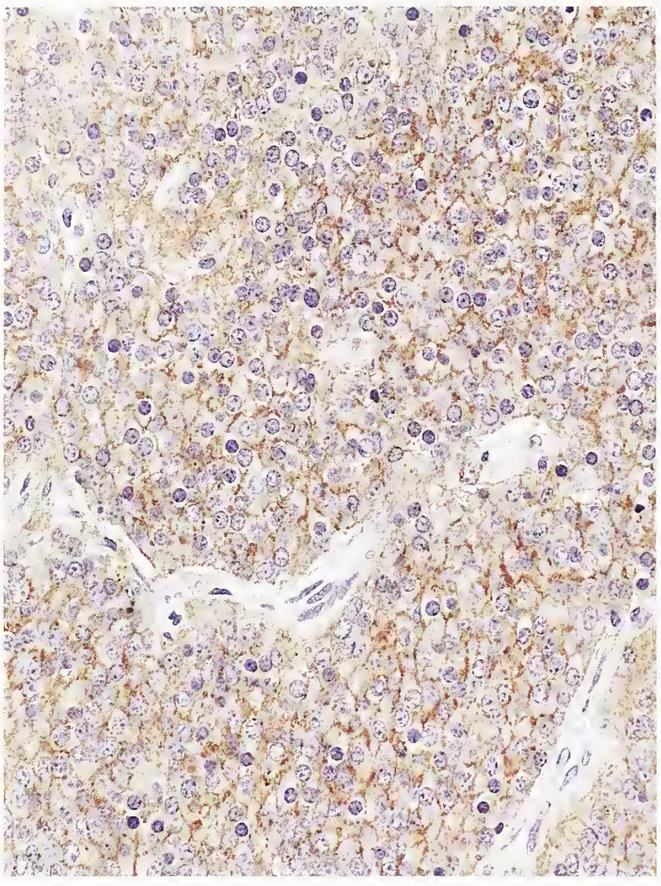


Figure 3-158
CARCINOID TUMOR WITH NEURAL CELL ADHESION MOLECULE (N-CAM)
The cell membrane of almost all tumor cells is strongly immunoreactive for N-CAM. (Immunostaining after cold acetone fixation and paraffin embedding)

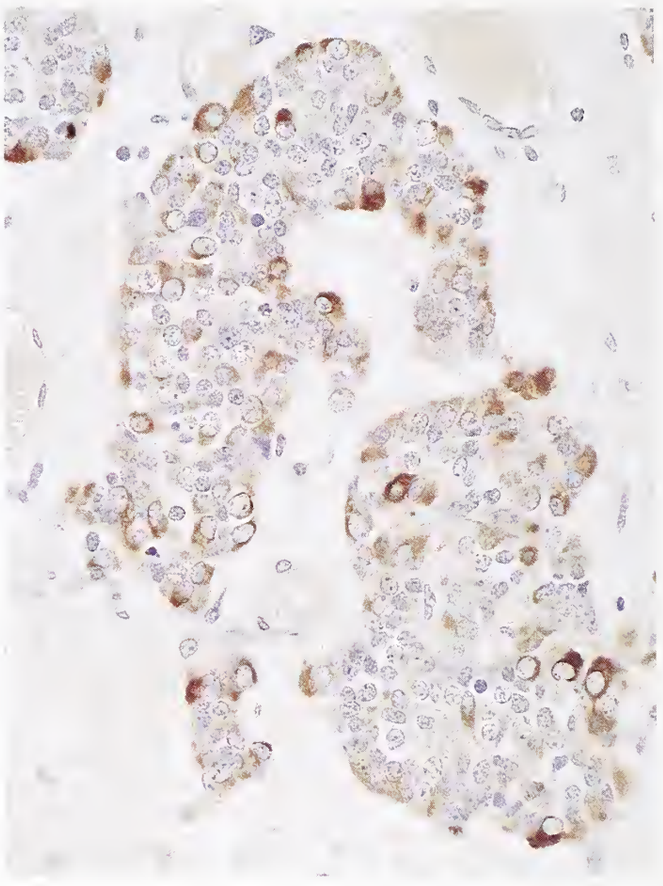


Figure 3-159
CARCINOID TUMOR WITH IMMUNOREACTIVE SOMATOSTATIN
Tumor cells, particularly those at the periphery of tumor nests, are strongly immunoreactive for somatostatin (same case as that in figures 3-140, 3-141).

in metastases obtained at autopsy. Negative immunostaining is probably due to secretion of the product soon after production in this case. The tumors showed strong immunohistochemical positivity for NSE, moderate positivity for chromogranin A and Grimelius argyrophilia, and only focal positivity for cytokeratin, synaptophysin, and S-100 protein (sustentacular cells only).

Takayama et al. (175) reported a case of "atypical" thymic carcinoid tumor (carcinoid tumor by our definition) which contained a significantly high level of calcitonin, whole human chorionic gonadotropin (hCG), and parathyroid hormone (PTH). The patient was a 34-year-old woman who developed an unresectable anterior mediastinal tumor and died of systemic metastases 10 months after exploratory thoracotomy. The surgically obtained tumor revealed large solid nests and diffuse growth of medium-sized, rather uniform cells with oval hyperchromatic nuclei, distinct nucleoli, scanty cytoplasm, and frequent mitotic figures (fig. 3-161). Grimelius argyrophilia was noted, as well as positive immunostaining for NSE, chromogranin A, protein gene product 9.5 (PGP9.5) and beta-hCG (fig. 3-162). However, calcitonin, PTH, parathyroid hormone-related protein (PTHrP), calcitonin gene-related peptide, ACTH, GRP, serotonin, and pancreatic polypeptide were negative, and there were no features of choriocarcinoma. The resected tumor tissue contained 9600 mIU hCG (whole), 140 ng calcitonin, and 66 μg/g wet weight NSE. Midregion PTH was 83 ng, C-terminal PTH 1.7 ng/g wet weight, and N-terminal PTH was undetectable. The autopsy revealed diffuse parathyroid hyperplasia and multiple islet cell tumors of the pancreas. MEN type I associated with thymic carcinoid was considered, although the pituitary gland was not

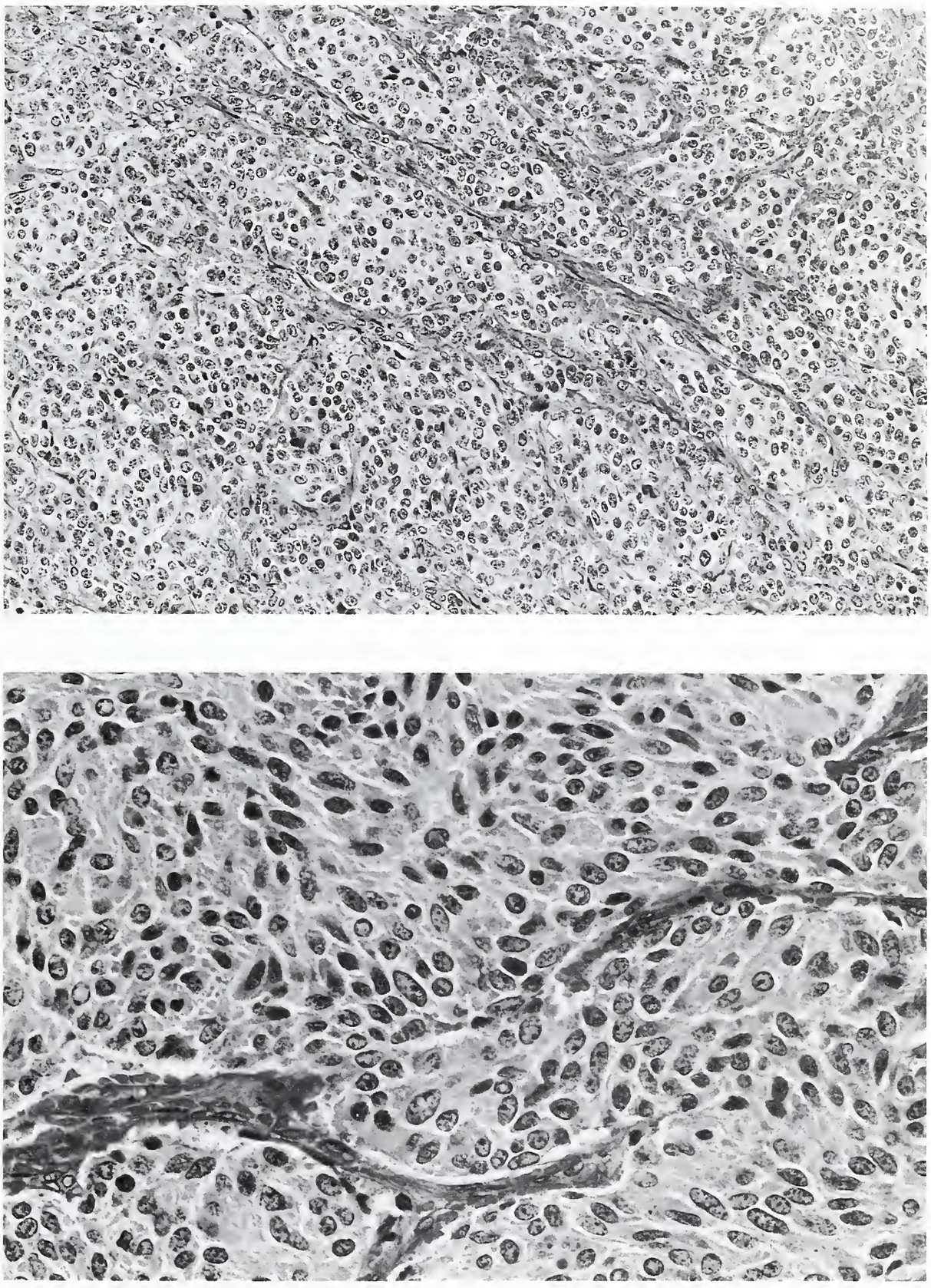


Figure 3-160
CARCINOID TUMOR WITH ECTOPIC ACTH PRODUCTION

This mediastinal tumor is composed of various sized nests of polygonal to spindle cells with round to oval nuclei and finely granular cytoplasm supported by delicate blood vessels. Initially the tumor was silent endocrinologically, but showed signs of ACTH production when it recurred. However, ACTH could not be demonstrated immunohistochemically in either the primary or the metastatic tumor. Top: low-power view; bottom: high-power view. (Courtesy of Dr. Koji Chihara, Shizuoka, Japan.)

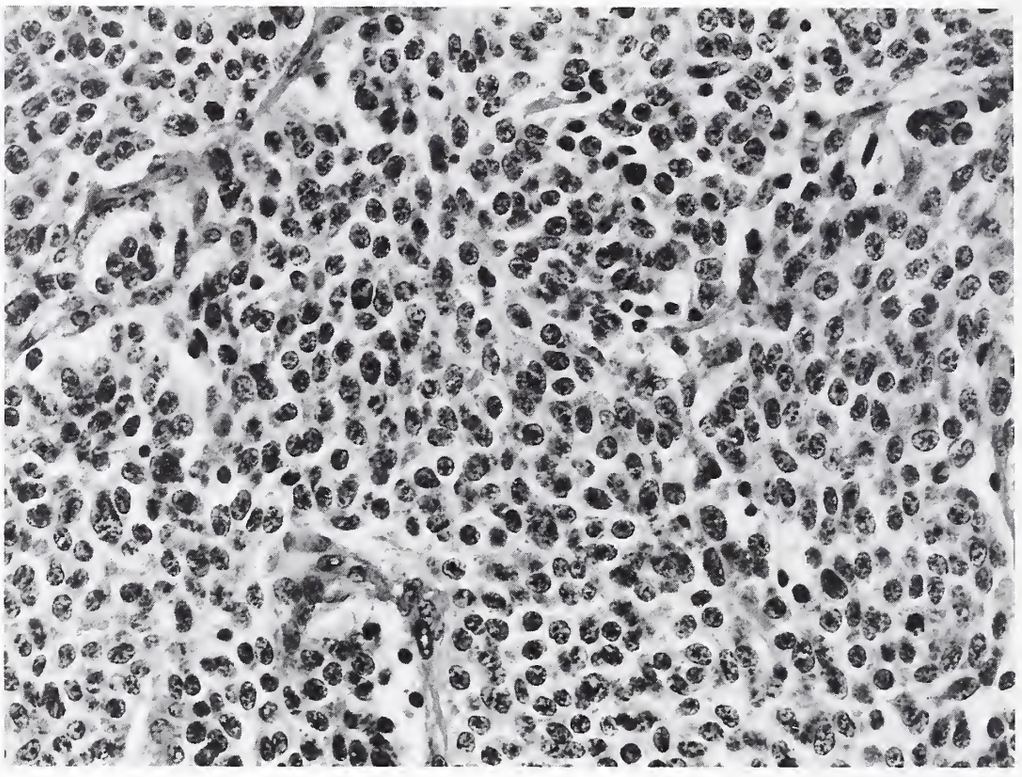


Figure 3-161
CARCINOID TUMOR PRODUCING BETA–HUMAN CHORIONIC GONADOTROPIN
Oval tumor cells with slight nuclear atypia and distinct nucleoli are intimately associated with delicate blood vessels. (Figures 3-161 and 3-162 are from the same case.) (Courtesy of Dr. Toru Kameya, Sagamihara, Japan.)

examined. This was the first reported case of thymic carcinoid tumor producing hCG and PTH.

Apart from bioactive substances, N-CAM is always detected in thymic carcinoid tumor (fig. 3-158). However, the value of N-CAM as a marker of neuroendocrine tumors is reduced by its antigenic lability in formalin-fixed tissue. With regard to cytoskeletal components, carcinoid tumor cells contain immunoreactive low molecular weight cytokeratin, which is often demonstrated in the paranuclear region (fig. 3-163), probably corresponding to whorls of cytoplasmic fibrils. S-100 beta-positive sustentacular cells may be present focally in a typical primary tumor (figs. 3-148, 3-164) (158), but has been absent in metastatic tumors examined so far. Therefore, it is considered that sustentacular cells may be lost during growth of the tumor, along with loss of an organoid arrangement.

With regard to proliferative activity, cells positive for proliferating cell nuclear antigen (PCNA) are frequently found even in a tumor with only occasional mitotic figures. In such tumors, the frequency of stained nuclei is higher in areas composed of more atypical cells, and staining may be absent in some rosettes (fig. 3-165), indicating that rosette-forming tumor cells may have reduced proliferative activity.

Differential Diagnosis. If characteristic tumor cells are arranged in an organoid pattern, diagnosis is easy. If the organoid pattern is vague, areas on multiple sections where the histology is typical of carcinoid tumor should be sought, and immunohistochemistry done to exclude poorly differentiated carcinoma, malignant lymphoma, and some germ cell tumors, and disclose the presence of neuroendocrine markers.

Occasional diagnostic difficulty is encountered when individual tumor cells are larger and more atypical than usual carcinoid tumor cells (fig. 3-146C, 3-166). Such tumors are called "atypical" carcinoid by some pathologists, but we believe it is better to designate them as nonsmall cell or large cell neuroendocrine carcinomas, unless features of typical carcinoid tumor are evident elsewhere.

Epithelial cell predominant thymoma may mimic thymic carcinoid tumor if the former has a rosette-like structure or is composed of short spindle cells with a finely granular cytoplasm (see figs. 3-60, 3-61). Rosette-like structures in thymoma are frequently associated with lymphocytes, but rarely so in carcinoid tumors. In a difficult case, immunohistochemistry is helpful for diagnosis. Rarely, structures resembling perivascular spaces are seen in carcinoid tumor; these are often artifacts.

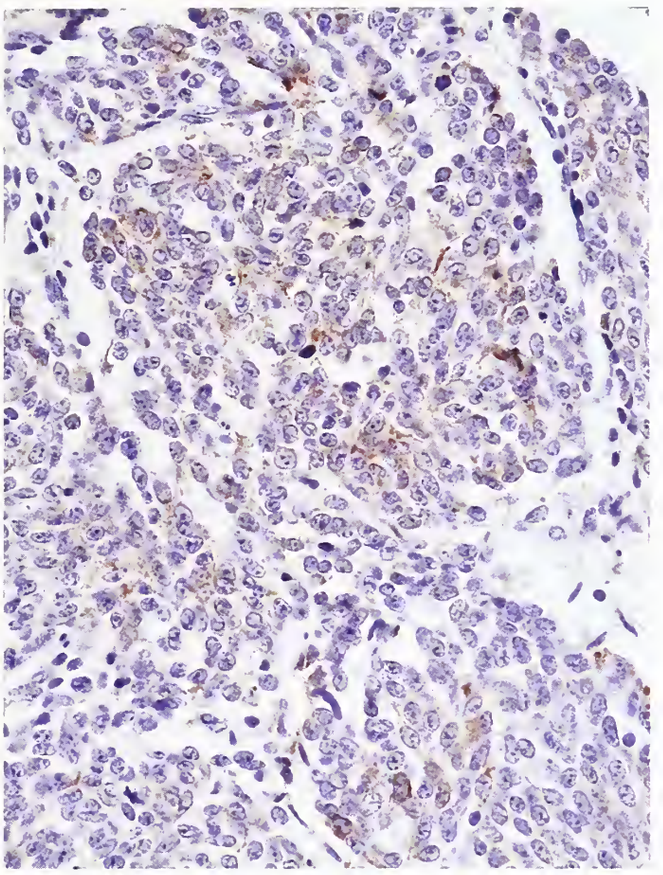


Figure 3-162
CARCINOID TUMOR WITH IMMUNOREACTIVE BETA–HUMAN CHORIONIC GONADOTROPIN

The tumor cell cytoplasm is variably immunostained for beta-hCG. Note that there are no features of choriocarcinoma.

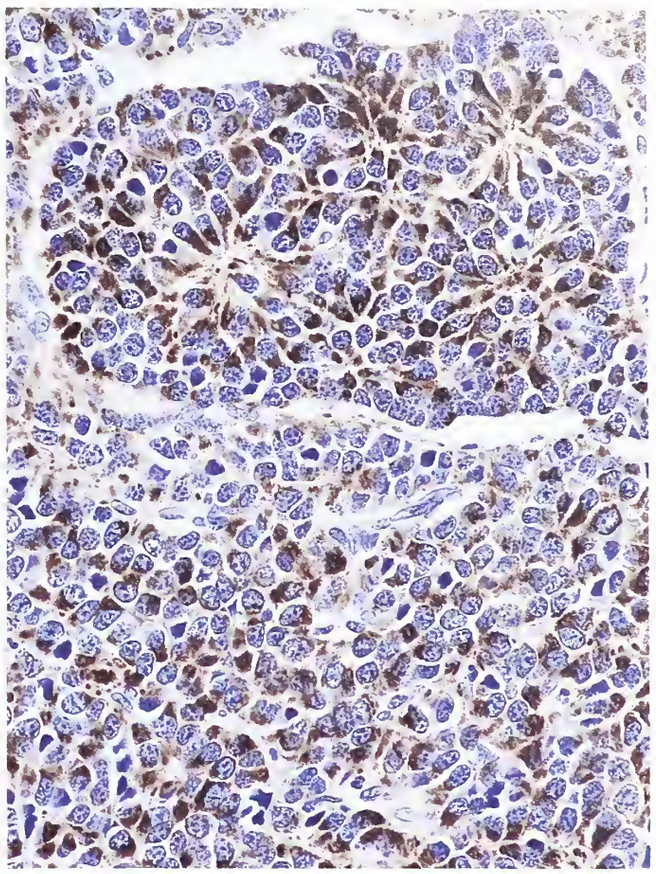


Figure 3-163
CARCINOID TUMOR WITH IMMUNOREACTIVE CYTOKERATIN

Tumor cells in both solid cell nests and rosettes show intense immunoreactivity for cytokeratin in the paranuclear region. (Courtesy of Dr. Noboru Mohri, Tokyo.)

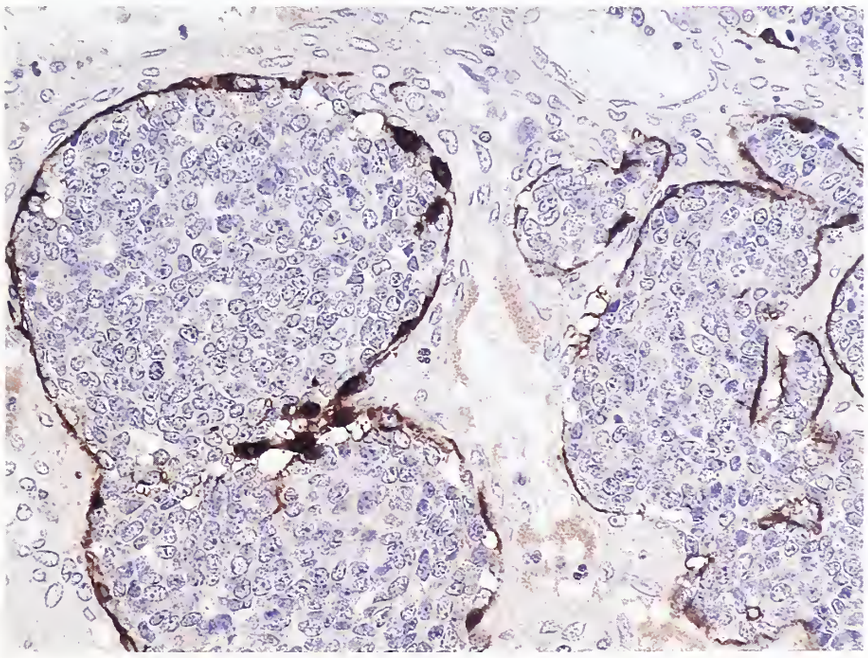


Figure 3-164
CARCINOID TUMOR WITH S-100 PROTEIN–POSITIVE SUSTENTACULAR CELLS

Solid tumor cell nests are bordered by elongated cells, which are intensely stained for S-100 beta-protein. Cell nests with sustentacular cells were limited to small areas of the primary tumor, and were not evident in tumors that recurred 10 years later (same case as that in figure 3-148). (Courtesy of Dr. Tadakazu Shimoda, Tokyo.)

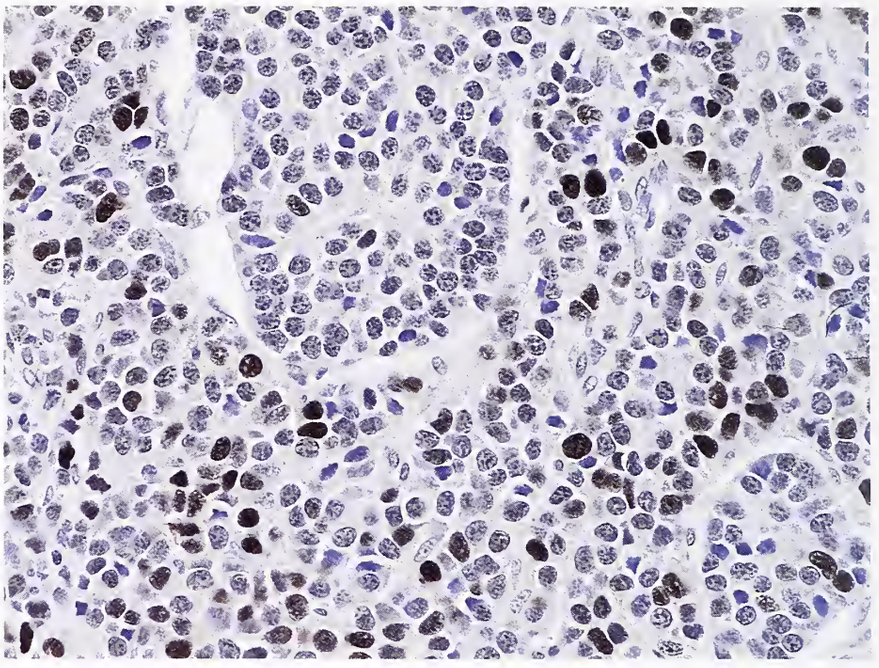


Figure 3-165
CARCINOID TUMOR SHOWING PROLIFERATING CELL NUCLEAR ANTIGEN (PCNA)

Slightly less than half of the tumor cells show nuclear staining for PCNA, but only a few positive cells are noted in areas with rosettes (same case as that in figure 3-163). (Courtesy of Dr. Noboru Mohri, Tokyo.)

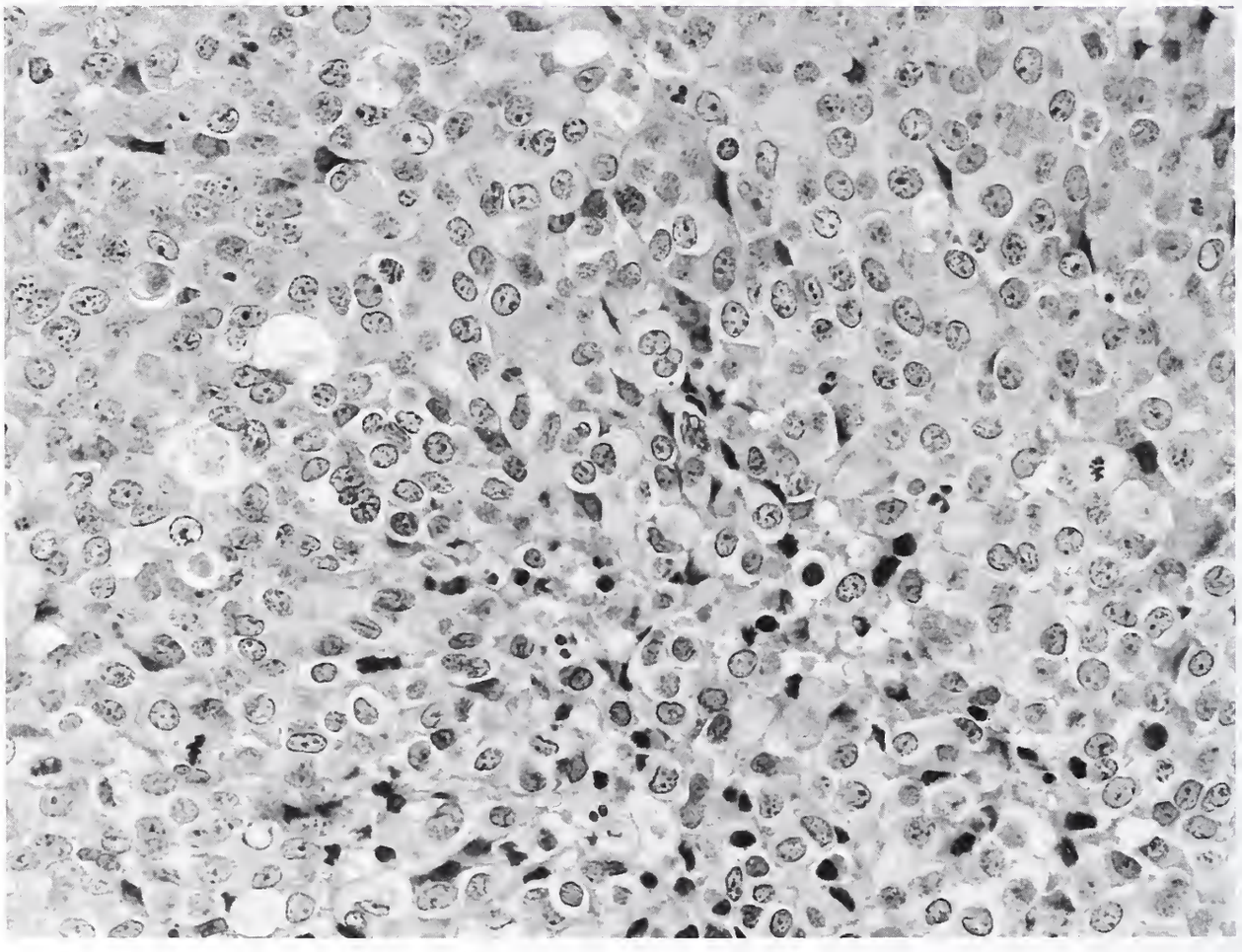


Figure 3-166
CARCINOID TUMOR WITH CELLULAR ATYPIA

The tumor consists of diffuse growth of moderately large cells with round to oval finely granular nuclei, small nucleoli, and a moderate amount of ground-glass cytoplasm. A few mitotic figures and frequent pyknotic cells are present. Grimelius argyrophilia was evident. The tumor was inoperable and the patient died 2 years later with widespread metastasis. (Courtesy of Dr. Tetsuro Kodama, Kashiwa, Japan.)

When immunohistochemical findings are still inconclusive, electron microscopic examination disclosing neuroendocrine granules is diagnostic. Some thymic carcinoid tumors may produce unknown bioactive substances whose presence cannot yet be verified.

Treatment and Prognosis. The treatment of choice is surgical removal of the tumor. If the tumor is pT1 at stage I (see Table 3-10), adjuvant therapy may not be needed, but if the tumor is pT2 at stage I or higher, postoperative radiotherapy with or without chemotherapy is indicated. The prognosis of patients with paraneoplastic syndromes such as Cushing's syndrome is invariably poor. Even without such a syndrome, according to Wick et al. (179) the prognosis is worse than previously believed, in comparison with patients with carcinoid tumors of other organs. Of 15 patients, "11 had metastases and 8 of these were either dead or likely to die from the tumor." Among 4 patients without metastases, 2 died of Cushing's syndrome and 2 survived without recurrence for 1 year after surgery. In eight cases reported by Valli et al. (178), follow-up information was available in four: one stage I tumor (encapsulated tumor) showed local recurrence and lung metastasis within a year; the three patients with stage III tumor (invading neighboring organ) died of liver, bone, and brain metastasis within 3 years. Fourteen cases treated by de Montpréville et al. (159a) also revealed the poor prognosis of patients with large tumors, ranging from 6 to 20 cm, and tumors with a histologic appearance of atypical carcinoid. All patients died of disease within 109 months as a result of local progression, local relapse, distant metastases, or a combination of these. Median survival was 71, 30, and 5 months for patients who had total resection, partial resection, and simple biopsy, respectively. In 13 cases we examined, 1 patient died of unrelated disease, 1 died of tumor with ectopic ACTH production within 2 years after surgery, 3 patients with inoperable tumors including 1 showing hCG and PTH production died within 2 years, 2 with invasion into the lung and metastasis to lymph nodes were alive and free of disease for 5 and 2 1/2 years postoperatively, and 1 with a lymph node metastasis developed another node metastasis 12 years after surgery. Recurrence of the tumor, either locally or in distant organs, may become evident several years or more after removal of the primary. Frequent sites of metastasis include mediastinal lymph nodes, cervical lymph nodes, lung, and bone. Bone metastasis is often osteoblastic.

Figure 3-167
CARCINOID TUMOR WITH FEATURES OF THYMOMA
Grossly, the tumor is completely encapsulated and partly lobulated. (Figures 3-167 and 3-168 are from the same case.)

Probable Combined Thymoma and Carcinoid Tumor. We have seen a single example of probable combined carcinoid tumor and thymoma in an elderly man. The tumor was encapsulated and 4 cm in greatest dimension (fig. 3-167). Microscopically, lobulation by fibrous septa was apparent, and the tumor consisted of typical carcinoid tumor cells forming rosettes in some areas; solid nests of somewhat larger tumor cells, with finely granular eosinophilic cytoplasm resembling oncocytes in some areas; and polygonal to oval epithelial cells arranged in nests and sheets, with frequent dilated perivascular spaces resembling epithelial cell–predominant thymoma in other areas (fig. 3-168). The Grimelius silver reaction was positive only in rosette-forming and oncocytoid cells. NSE was positive in limited areas, and rare cells containing pancreatic polypeptide and calcitonin were found. All other neuroendocrine markers tested were negative, including N-CAM, chromogranin A, synaptophysin, somatostatin, GRP, serotonin, and ACTH. Electron microscopic examination of paraffin-embedded tissue demonstrated that some cells were equipped with tonofibrils and desmosomes but not with membrane-bound electron-dense granules,

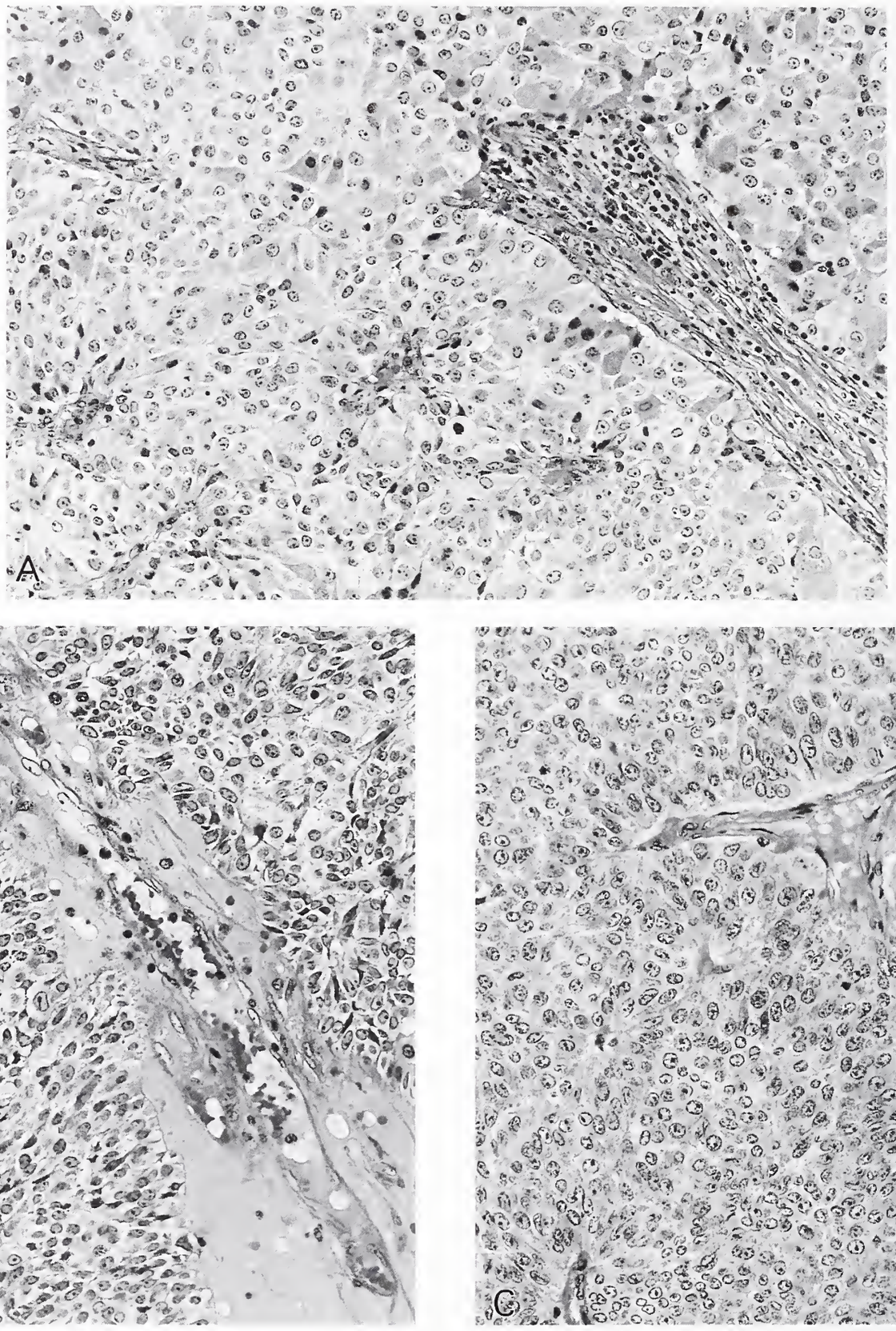


Figure 3-168

CARCINOID TUMOR WITH FEATURES OF EPITHELIAL CELL PREDOMINANT THYMOMA

A: The tumor is incompletely lobulated by fibrous septa, and composed of oval to polygonal cells with oval nuclei and small but distinct nucleoli forming rosettes. Some tumor cells possess abundant eosinophilic cytoplasm and resemble oncocytes.

B: In some areas, there are cystic spaces (left lower corner) and perivascular spaces with a few lymphoid cells.

C: In other areas, oval to short spindle tumor cells with distinct nucleoli show diffuse growth and palisading around blood vessels, resembling predominantly epithelial thymoma.

whereas other cells contained electron-dense granules of the neuroendocrine type without features of thymic epithelial cells. Although precise ultrastructural analysis could not be done because of the unavailability of well-fixed tumor tissue, this case certainly suggested a combination of carcinoid tumor and thymoma. The presence of such a tumor in the thymus indicates that the tumor develops from primitive multipotential (or bipotential) cells, supporting the concept of histogenesis of carcinoid tumor described previously (173). Coexistence of thymoma in the right lobe and carcinoid tumor in the left lobe of the thymus has been reported by Mizuno et al. (167).

Kuo (165) reported a case of carcinoid tumor with divergent sarcomatoid differentiation. The tumor was composed of nests of carcinoid tumor cells in a sarcomatous stroma characterized by fibrosarcoma-like spindle cells with areas of chondroid and osseous differentiation. Areas with features of carcinoid tumor were reported to be positive for NSE, vimentin, and cytokeratin; very weakly positive for synaptophysin and somatostatin; and negative for chromogranin, ACTH, and calcitonin. Ultrastructurally, the spherical granules were much smaller than those in carcinoid tumor.

GERM CELL TUMORS

Definition and Classification. A germ cell tumor is believed to develop from a germ cell during the process of maturation of a primordial germ cell into a gamete. It can arise not only in the gonad but also in the midline of the body, such as in the intracranial pineal region, anterior mediastinum, retroperitoneum, and sacrococcygeal region, where germ cells migrate during embryogenesis and sometimes become misplaced (ectopic germ cells). Since the thymus is located in the midline of the thorax, it is easily understood that a germ cell tumor may develop within or in the proximity of the thymus. In fact, almost all mediastinal germ cell tumors are found either within or adjacent to the thymus. However, this "misplacement" theory has not been proved, and germ cell tumors could well originate from the primordial cells of the thymus, that is, through anaplasia of the primitive thymic epithelial cells to form totipotential cells. In support of this theory, Kaplan et al. (190) reported that "extragonadal teratomas arise mitotically from diploid cells and no heterosexual (XX) tumors were seen in males, which would be expected in parthenogenetic tumors."

Table 3-12

CLASSIFICATION OF TERATOMAS*

I. Benign teratomas
   A. Mature teratoma:
      Grade 0 (All component tissues appear well differentiated)
      Grade 1 (Occasional microscopic foci contain incompletely differentiated tissues, not exceeding 10 percent of the sampled surface)
   B. Immature teratoma, benign:
      Grade 2 (Immature tissues make up between 10 and 50 percent of the sampled tumor surface)
      Grade 3 (Over half the surface examined is composed of undifferentiated tissues of uncertain metastatic potential. A benign course is still possible)

II. Malignant teratomas
   A. With areas of germ cell tumor:
      Germinoma (seminoma, dysgerminoma)
      Embryonal carcinoma
      Choriocarcinoma
      Yolk sac tumor
      Mixed (any combination of the above)
   B. With nongerminal malignant tumor pattern:
      Carcinoma
      Sarcoma
      Malignant embryonal tumor
      Mixed
   C. Immature teratoma, malignant:
      A teratoma that would otherwise be classified as benign immature teratoma, but which subsequently became metastatic

*From reference 186.

Every form of germ cell tumor occurs in the mediastinum: teratoma (mature, immature, and with malignant transformation), germinoma (seminoma or dysgerminoma), embryonal carcinoma, yolk sac tumor (endodermal sinus tumor), choriocarcinoma, and mixed germ cell tumor. The histology is essentially similar to that of germ cell tumors of the gonads. The tentative classification of teratoma by Gonzalez-Crussi (186), which appears useful in practice, is shown in Table 3-12 (186).

Incidence and Clinical Findings. The anterior mediastinum is the most frequent site of extragonadal germ cell tumors. The number of germ cell tumors of the mediastinum surgically resected at the National Cancer Center Hospital, Tokyo, was slightly lower than that of thymomas (60 versus 79) (Table 3-3), and accounted for 14 percent of all gonadal and extragonadal germ cell tumors resected; the remaining germ cell tumors were testicular (42 percent), ovarian (40 percent), sacrococcygeal (2 percent), intracranial (1 percent), and retroperitoneal (1 percent). However, this incidence varies depending upon the type of institution reporting.

Table 3-13 indicates the types of germ cell tumors that have been surgically resected. Mature teratoma accounts for about 75 percent of the total, and is found in patients of all ages but most frequently in adolescents. In females, all the tumors are mature teratomas, mostly cystic. Immature teratoma, the pure form of which accounts for about 1 percent and the mixed form 10 to 20 percent of all mediastinal germ cell tumors, is more frequent in children and adolescents. Malignant teratoma and other malignant germ cell tumors, such as germinoma (seminoma), yolk sac tumor, and choriocarcinoma, which represent 25 percent of all mediastinal germ cell tumors, developed exclusively in males, as was the case for immature teratoma in our series.

Mature teratomas are often clinically silent and found frequently by chest X-ray examination. However, some patients may complain of cough, dyspnea, or chest pain, which are due to compression of the airways and other structures by large mediastinal teratomas. Rarely, patients cough up the contents of the tumor, including hair. This happens after destruction of the bronchi, probably as a result of friction and compression of the lung tissue by the tumor (fig. 3-169).

Most patients with immature teratoma, malignant teratoma, and other malignant germ cell tumors are symptomatic at the time of diagnosis, presenting not only with cough, dyspnea, or chest pain due to compression of organs by the rapidly growing tumor, but also with fatigue and weight loss. Gynecomastia may be evident when the tumor contains choriocarcinoma.

Patients with Klinefelter's syndrome are predisposed to develop germ cell tumors, particularly those of extragonadal origin (196). Lachman et al. (192) in their review of the literature stated that there were 20 cases of primary mediastinal germ cell tumor associated with Klinefelter's syndrome and 252 cases of primary mediastinal germ cell tumor in the normal male population. The incidence rate of Klinefelter's syndrome among patients with mediastinal germ cell tumor is

Table 3-13

SURGICALLY RESECTED GERM CELL TUMORS*

	No. of Cases (age) Male	Female
Benign teratoma	19	26
MT (or with IMT)**	19 (6–54)†	26 (11-60)
Malignant teratoma	12	
MT + IMT + necrosis	1 (15‡¶)	
MT + IMT + YST	2 (15,25)	
MT + IMT + YST + Ger + Ad	1 (17)	
MT + IMT + Ad + CaSa + NB	1 (39¶)	
MT + YST	1 (58)	
MT + Em	1 (27)	
IMT + Ger	1 (17¶)	
IMT + Ger + Ad	1 (24)	
IMT + YST	1 (17§)	
YST + Ger	1 (29)	
Entirely necrotic tumor	1 (24‡¶)	
Ger	1 (21¶)	
Cho	2 (15¶,22)	
Totals	34	26

*National Cancer Center, Tokyo 1962–1992.
**MT: mature teratoma; IMT: immature teratoma; YST: yolk sac tumor; Ger: gebminoma; Em: embryonal carcinoma; Cho: choriocarcinoma; Ad: adenocarcinoma; CaSa: carcinosarcoma; NB: neuroblastoma.
†Including three grade 1 and one grade 3 tumors.
‡With elevated serum alpha-1 fetoprotein and beta-hCG, and treated with antitumor agents.
§Died of acute leukemia 9 months after surgery.
¶Living with no evidence of disease more than 1 1/2 years.
During the same period, five patients treated without surgery were autopsied (two cases of YST, and one case each of Em, Ger, and IMT + Ca). All were male with ages of 27, 31, 33, 39, and 43 years. A case of IMT + Ca was complicated with malignant histiocytosis. One patient with YST and Ger diagnosed by biopsy died of tumor (no autopsy) and one patient with Ger diagnosed by biopsy is living and well.

Figure 3-169
MATURE TERATOMA INVADING THE LUNG
Polypoid tumors occlude and distend a bronchus. The tumor surface is opaque to semitranslucent, with mature fat and cartilage at the cut surface.

roughly 30 to 40 times that of Klinefelter's syndrome among the general population. Almost all kinds of germ cell tumors, both benign and malignant, occur in patients with the syndrome.

Association of hematologic malignancies with mediastinal germ cell tumors was discussed by de Ment (184), who reviewed 16 cases with simultaneous presentation, and 19 cases of hematologic malignancies that developed 48 months or longer after chemotherapy for mediastinal germ cell tumor. Such occurrence is greater than would be expected by chance alone, and de Ment et al. proposed two hypotheses: that hematopoietic malignancies arise from pluripotent germ cells and that alternatively, teratocarcinoma cells may elaborate factor S, which promotes the growth and differentiation of leukemic blast cells. The most frequent synchronous hematologic malignancy seen by de Ment was malignant histiocytosis, followed by acute myelomonocytic leukemia. Many cases of the former were reclassified recently as Ki-1 lymphoma. We have also seen one case each of acute leukemia and malignant histiocytosis (Table 3-13). Hematologic malignancies that develop after chemotherapy for germ cell tumors include acute myelogenous leukemia, acute megakaryocytic leukemia, and acute myelomonocytic leukemia.

Diagnostic Approach. Posterior-anterior and lateral chest roentgenograms frequently reveal a large round or nodular mass in the anterior or anterosuperior mediastinum, in many instances displacing and at times invading the adjacent structures such as the trachea, lung, and major vessels (fig. 3-170). Areas of calcification may be seen in the tumor. Pleural effusion may be present in patients with malignant germ cell tumors. Occasionally, air accumulates within the tumor, if the tumor communicates with the trachea or bronchus (fig. 3-171). The roentgenologic findings are not specific for germ cell tumor, and differentiation from other thymic tumors may be impossible. CT is useful for detection of small tumors which are not seen in routine chest roentgenograms. Whenever an anterior (or superior) mediastinal tumor is detected in male patients, a serologic study for tumor markers should be done, including hCG for choriocarcinoma and alpha-1 fetoprotein for yolk sac tumor.

For histologic confirmation of the nature of the tumor, a needle biopsy can be done either percutaneously or through a mediastinoscope (figs. 3-172–3-174). When the lung is invaded, transbronchial biopsy can also be attempted.

Teratoma. Grossly mature teratomas are often cystic and rarely predominantly solid (figs. 3-171, 3-175). They are encapsulated and occasionally adhere to the surrounding structures with fibrous tissue. The cut surface reveals a variegated appearance; unilocular or multilocular

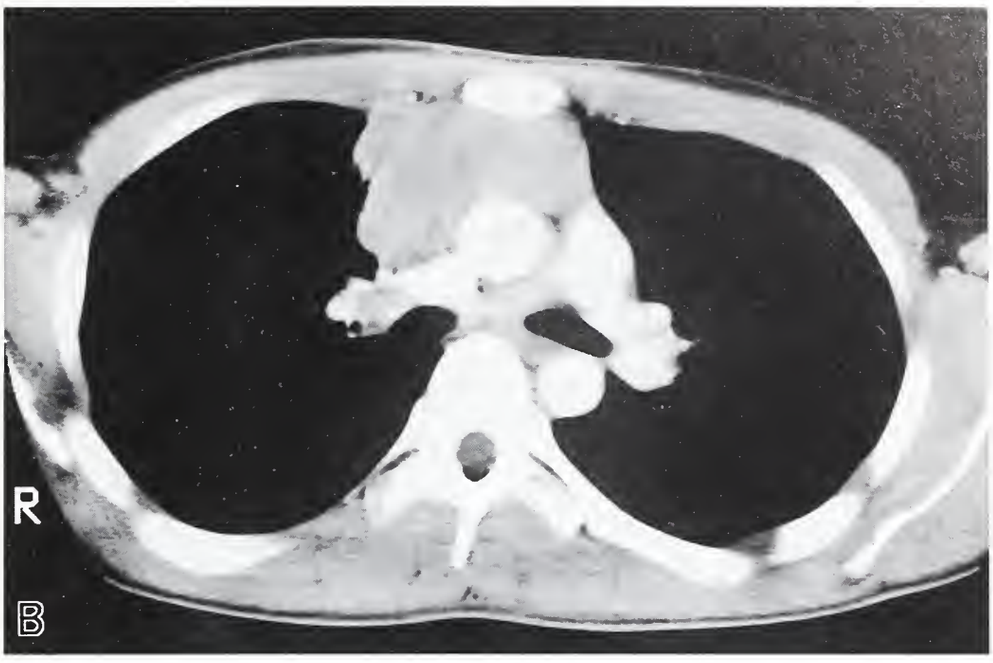
Figure 3-170
GERMINOMA (SEMINOMA)

A: A plain chest X-ray film reveals a tumorous density projecting toward the right lung from the right pulmonary hilum to the superior mediastinal region.

cavities containing brown fluid or oily or grumous materials with or without hair. In the cyst walls or solid areas, fatty tissue, medullary soft tissue, and flecks of cartilaginous tissue can be identified. When the tumor invades the lung, mature teratoma tissue may be exposed in the bronchial lumen (fig. 3-169).

Immature teratomas and malignant germ cell tumors are very often large, at times weighing over 1 kg. They are solid and frequently adhere to or invade the adjacent structures and organs. The cut surface varies in appearance depending upon the constituent tissues, often being soft and medullary but sometimes fibrous or largely cartilaginous. Areas of hemorrhage and necrosis are present, and are often extensive in malignant germ cell tumors (figs. 3-176–3-178).

Microscopically, teratomas are neoplasms composed of an abnormal mixture of several tissues derived from more than two, and often three, embryonic layers, i.e., ectoderm, entoderm, and mesoderm. In mature teratoma of the mediastinum, skin and its appendages are found constantly, followed in order of frequency by bronchial tissue, gastrointestinal mucosa, smooth muscle, and fat (80 to 90 percent of cases); bone, cartilage, exocrine and endocrine pancreatic tissue (50 to 60 percent of cases); salivary gland and central nervous tissue including ependyma (20 to 30 percent of cases); and rarely, prostatic gland and



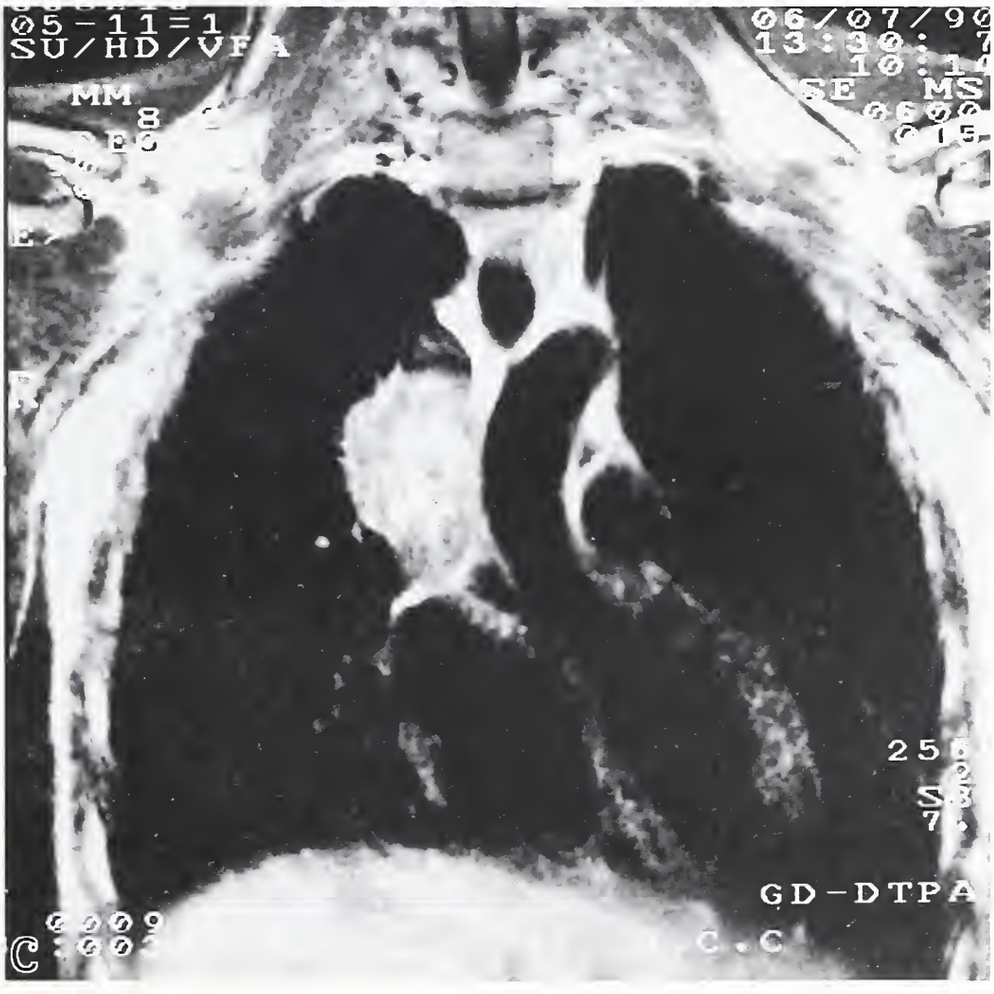


Figure 3-170 (Continued)

B: Enhanced CT with radiopaque material shows a retrosternal, well-defined tumorous density compressing the ascending aorta and superior vena cava posteriorly.

C: Thoracic MRI of a coronal section at the level of the ascending aorta reveals a nonhomogeneously enhanced tumor adjacent to the right border of the ascending aorta.

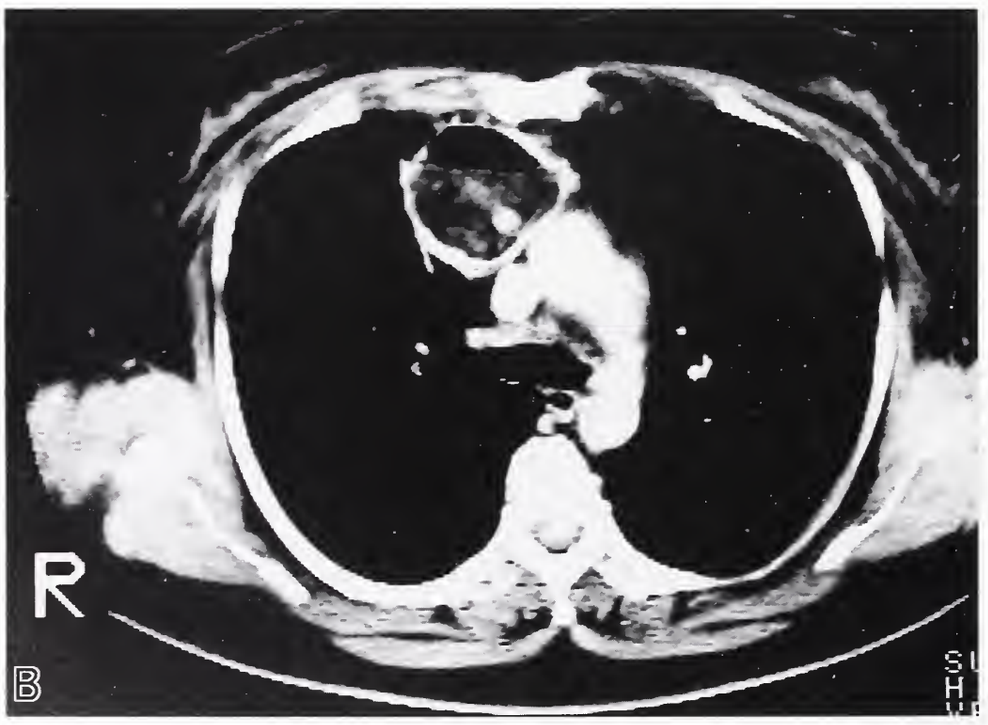


Figure 3-171
MATURE TERATOMA

A: Plain chest X-ray film reveals a large tumor projecting toward the right lung from the right pulmonary hilar region, which overlaps the right cardiac border. A close look shows free air near the superior border of the tumor.

B: CT enhanced with radiopaque material at the level of the tracheal bifurcation shows a tumor anterior to the ascending aorta and superior vena cava compressing the right lung. The tumor is irregularly stained and has a fluid level.

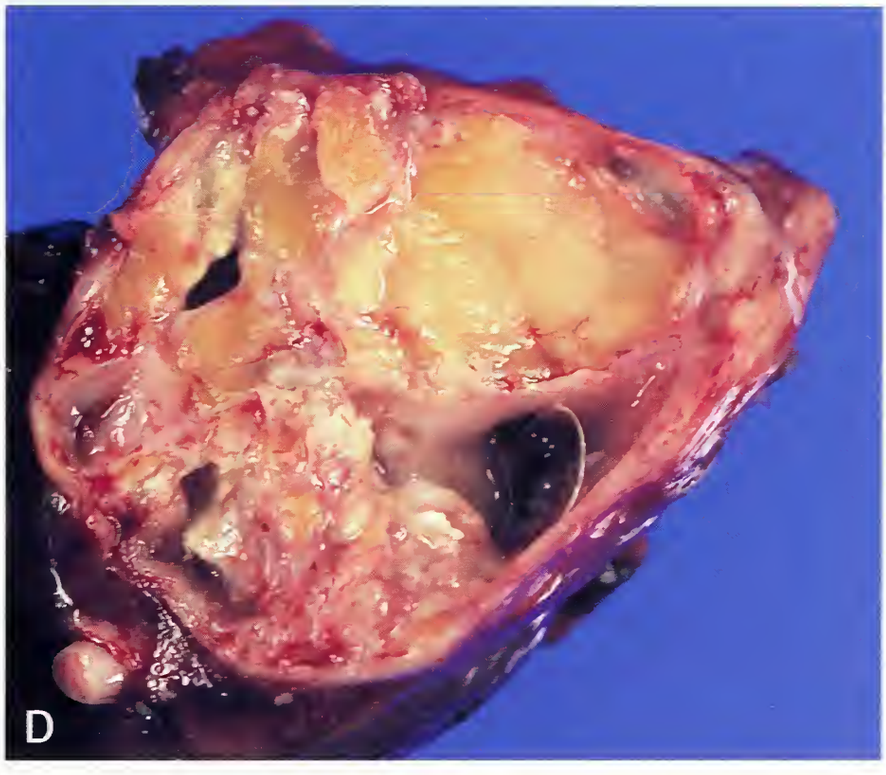


Figure 3-171 (Continued)

C: An enlarged CT view reveals engulfment of a B5 bronchus by the peripheral portion of the tumor, in which there are a few air spaces anteriorly and a ring-shaped calcification posteriorly on the right.

D: A horizontal slice of the resected tumor reveals fibrofatty tissue, calcified areas, and a few cystic spaces lined with smooth membrane and containing a hair. In the left lower corner, the involved B5 bronchus is evident.

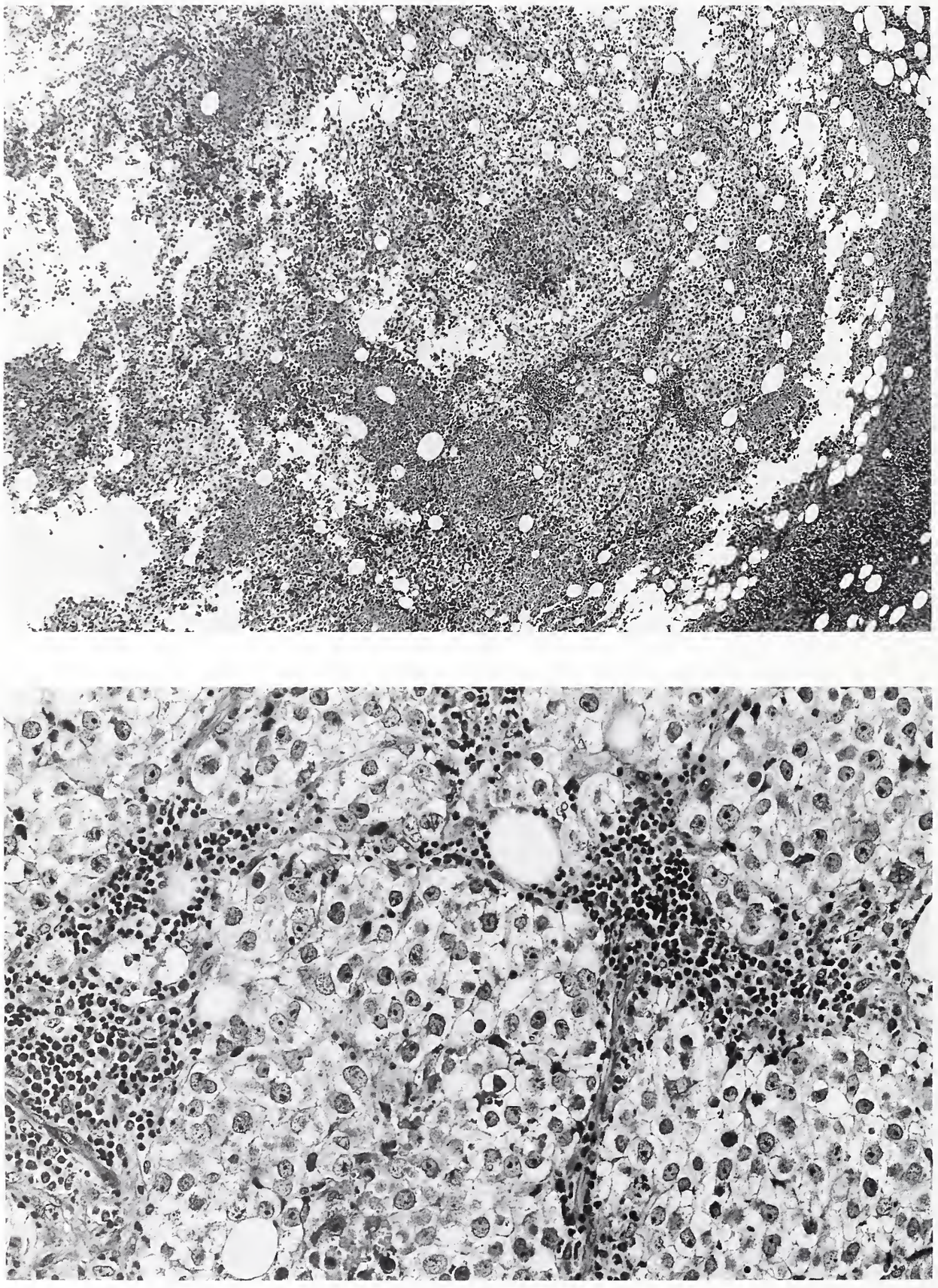


Figure 3-172
GERMINOMA DIAGNOSED BY PERCUTANEOUS NEEDLE BIOPSY

Partly necrotic tumor tissue infiltrates fatty tissue; the tumor tissue consists of solid nests of moderately large polygonal cells with clear cytoplasm, round nuclei, and prominent nucleoli, supported by a fibrous stroma densely infiltrated by lymphoid cells, features characteristic of germinoma (seminoma). (Top: low-power view; bottom: high-power view.)

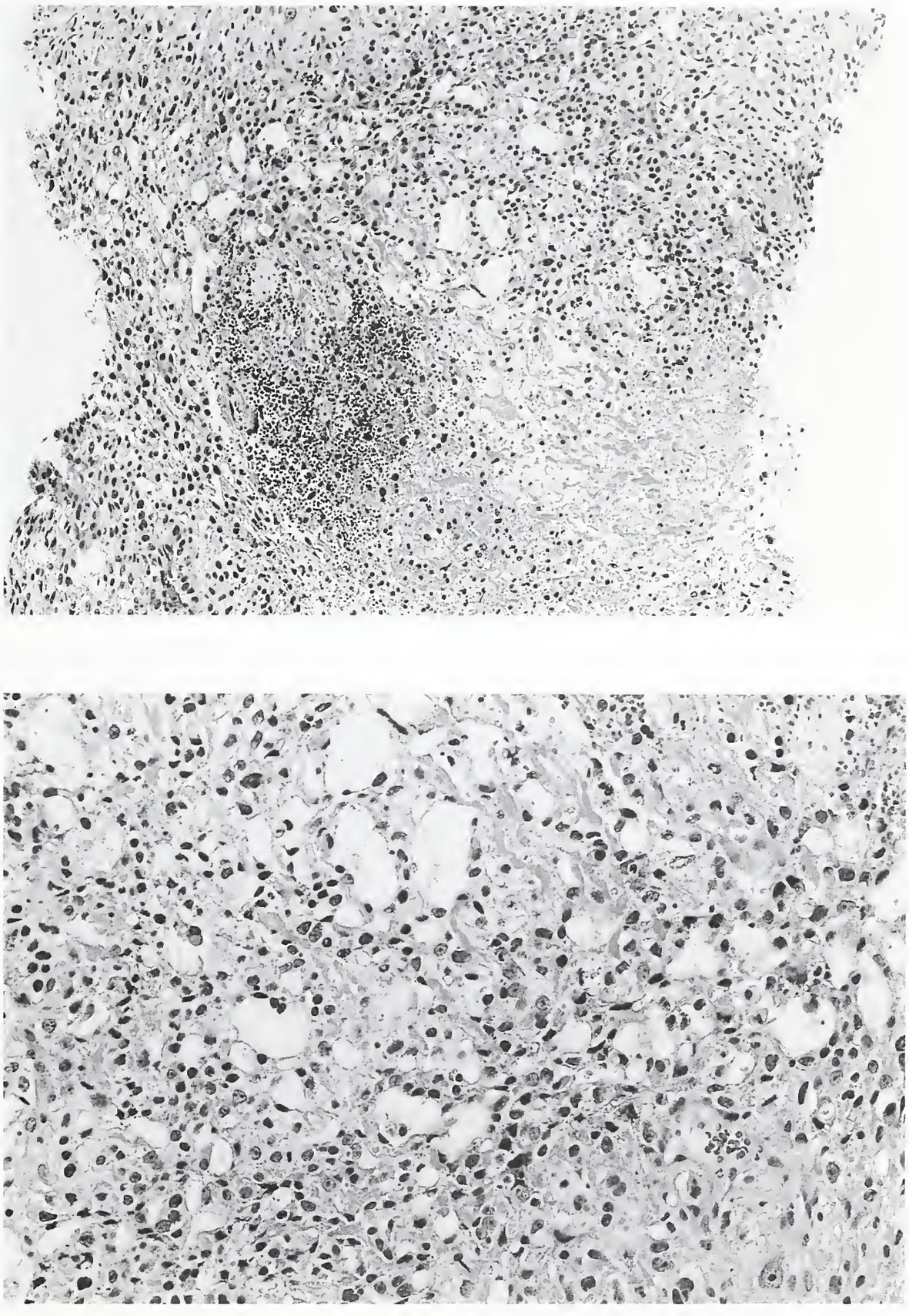


Figure 3-173
YOLK SAC TUMOR DIAGNOSED BY PERCUTANEOUS NEEDLE BIOPSY

The tumor is necrotic and hemorrhagic in some areas, showing a reticular pattern and solid growth. Intracellular and intercellular hyaline substances are also evident. These histologic features are characteristic of yolk sac tumor. (Top: low-power view; bottom: high-power view.)

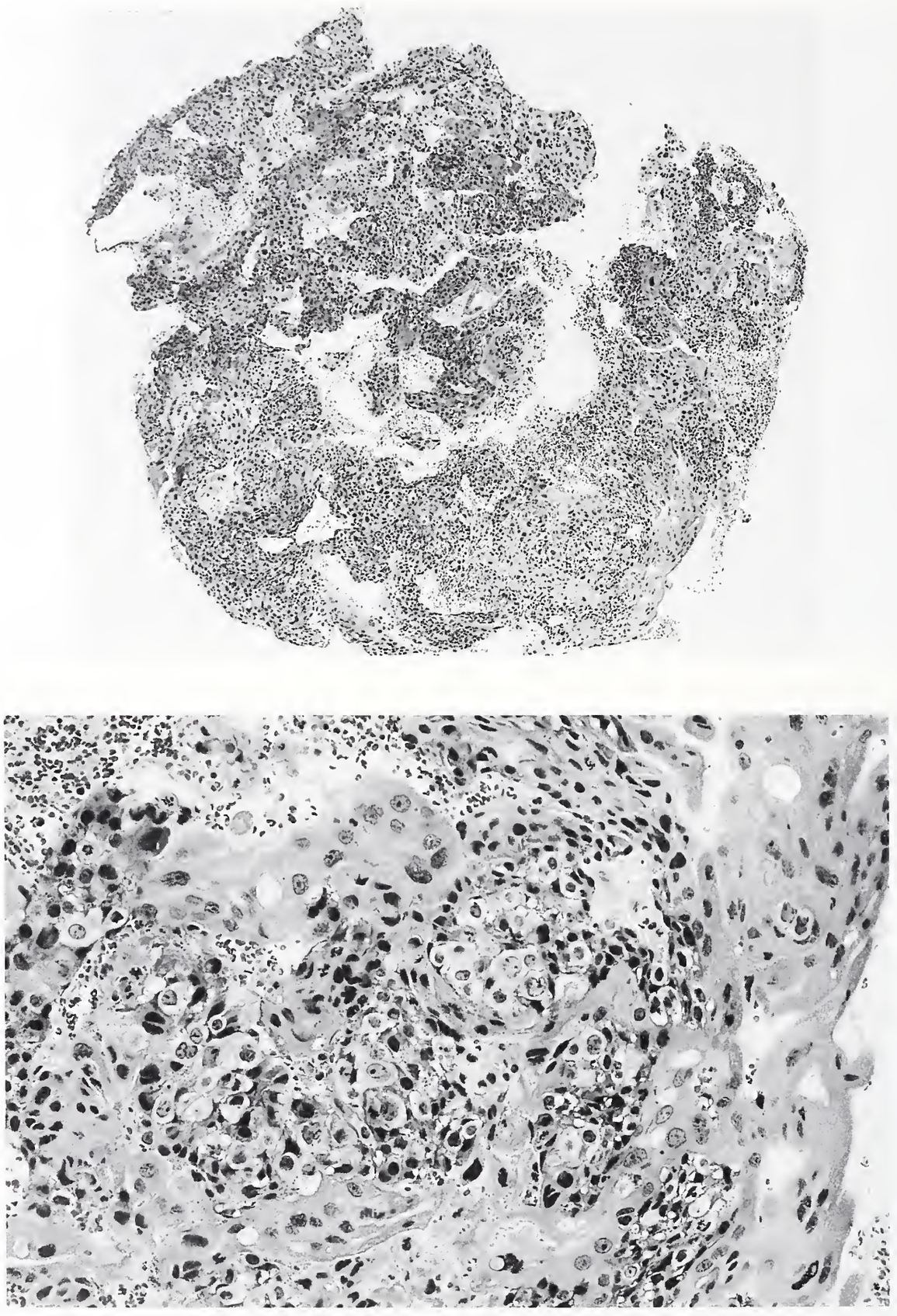


Figure 3-174
CHORIOCARCINOMA DIAGNOSED BY PERCUTANEOUS NEEDLE BIOPSY

A fragment consists largely of viable tumor tissue, and is composed of round to polygonal mononuclear cells resembling cytotrophoblasts and multinucleated cells with deeply eosinophilic cytoplasm resembling syncytiotrophoblasts. A diagnosis of choriocarcinoma was confirmed by positive beta-hCG immunostaining (see figure 3-190A). (Top: low-power view; bottom: high-power view.)

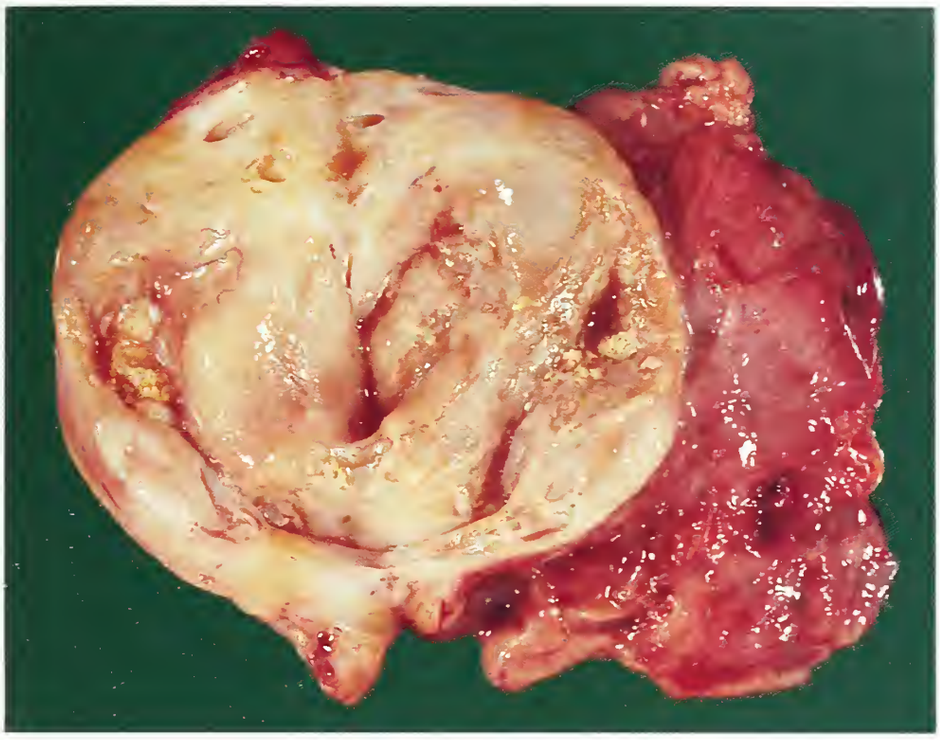


Figure 3-175
MATURE CYSTIC TERATOMA (DERMOID CYST)
The lining of the cyst is smooth in some areas and granular in others.

Table 3-14

FREQUENCY (%) OF THE PRESENCE OF ORGANS AND TISSUES IN MATURE TERATOMA OF MEDIASTINUM AND GONADS*

	Media-stinum	Ovary	Infant Testis
No. Cases Examined	**35**	**72**	**6**
Skin and adnexa	35 (100)	72 (100)	6 (100)
Bronchial mucosa and glands	30 (86)	45 (63)	6 (100)
Gastrointestinal mucosa	31 (89)	9 (13)	4 (67)
Pancreas (exocrine and endocrine)	19 (54)	0 (0)	0 (0)
Fat	28 (80)	39 (54)	6 (100)
Muscle	29 (83)	51 (71)	4 (67)
Salivary gland	11 (31)	15 (21)	4 (67)
Bone and cartilage	22 (63)	36 (50)	5 (83)
Nervous tissue	8 (23)	27 (38)	6 (100)
Melanin-containing cells	1 (3)	15 (21)	2 (33)
Hepatocytes	1 (3)	0 (0)	0 (0)
Thyroid	0 (0)	12 (17)	0 (0)

*National Cancer Center Hospital, Tokyo, 1962–1981.

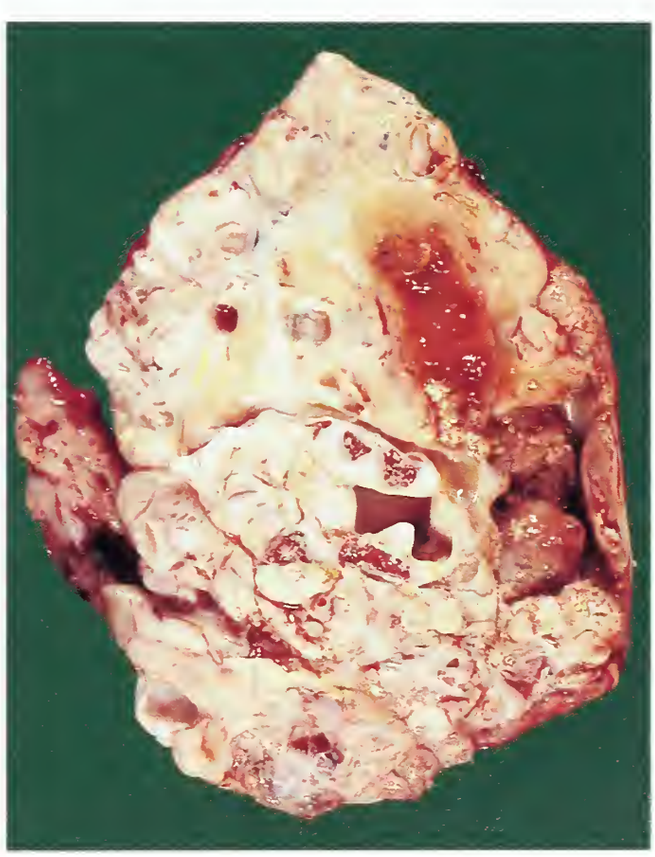


Figure 3-176
IMMATURE TERATOMA
A large immature teratoma shows a variegated appearance on cut section, corresponding to its constituent tissues.

Figure 3-177
MALIGNANT TERATOMA COMPOSED OF IMMATURE TERATOMA AND YOLK SAC TUMOR
An irregular large tumor is composed of abundant immature cartilage, which is present at the top of the photograph, and remaining extensive hemorrhagic and necrotic areas of yolk sac tumor.

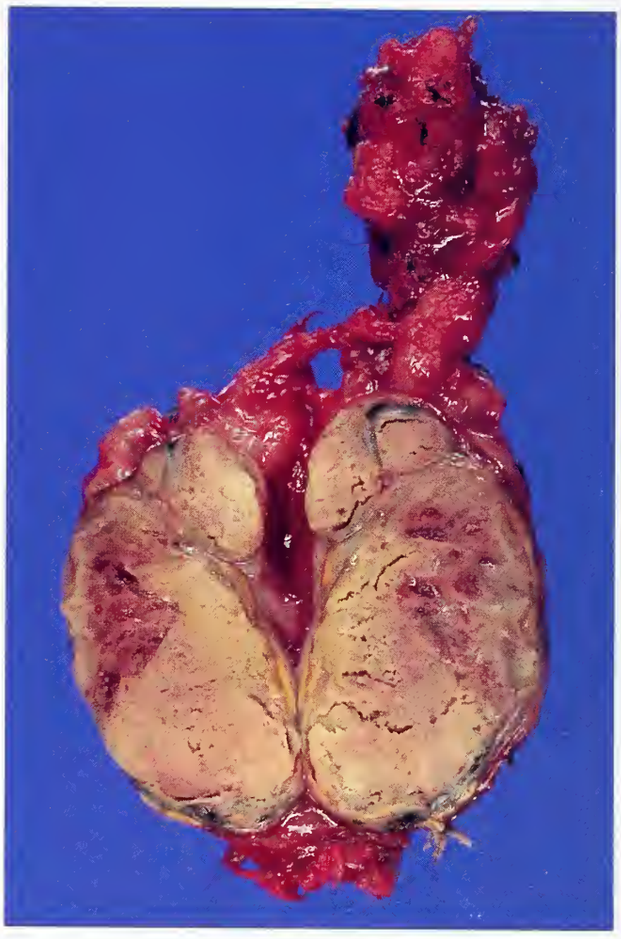


Figure 3-178
TREATED CHORIOCARCINOMA
The tumor is encapsulated and partly nodular, and its cut surface shows extensive coagulation necrosis and hemorrhage. No viable tumor cells could be identified histologically.

hepatocytes (Table 3-14; figs. 3-179–3-181). The presence of pancreatic tissue is of interest since it is not seen in teratomas of the gonads. Suda et al. (205) reported that among 17 teratomas with pancreatic tissue, 11 were located in the anterior mediastinum, 5 in the sacrococcygeal region, and 1 in the retroperitoneal space. A slightly low blood glucose level was found in one case and a very high level of amylase in the fistulous discharge from teratoma was found in another case. Bordi et al. (182) described a case showing the precise topographic distribution of endocrine cells that is seen in normal islets. Gastrointestinal tissue has also frequently been found in mediastinal teratomas. However, we have not yet seen thyroid follicles in mediastinal teratomas.

Mature teratoma is frequently cystic, with a lining often composed of dermal tissue or respiratory epithelium, and sometimes by foreign body type granuloma as a result of degeneration of the tumor.

We saw a teratoma in a 25-year-old male that contained lobules of mature glandular tissue which resembled prostatic or Skene's glands, although the basal cells were inconspicuous. The tissue was strongly positive for prostatic acid phosphatase, and scattered cells were intensely positive for prostate-specific antigen (PSA). Alcian blue-PAS stain revealed the presence of cytoplasmic mucus in some cells showing mucus cell metaplasia. Within the stroma, bundles of smooth muscle cells were found, as in the normal prostate, but in addition, a few spindle-shaped

Figure 3-179
MATURE TERATOMA
Between the epidermis and subcutaneous fat there are sebaceous and sweat glands, hair follicles, and smooth muscle, all of which are mature.

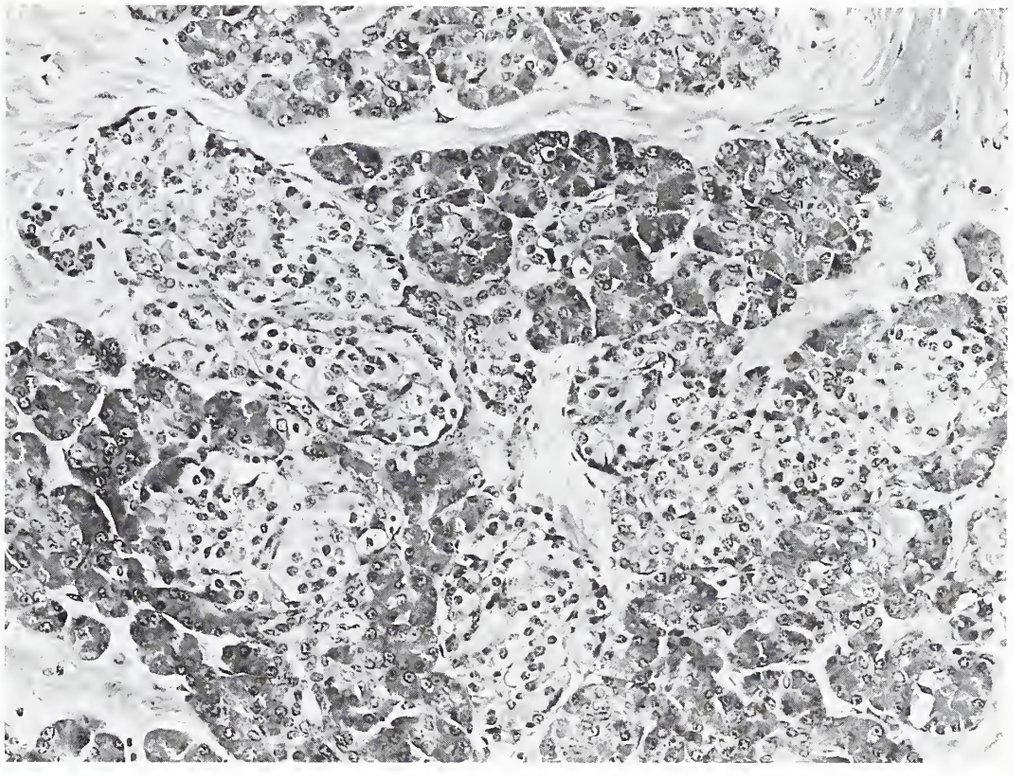


Figure 3-180
MATURE TERATOMA
Exocrine pancreatic acini and islets of Langerhans are evident.

melanocytes were also present (fig. 3-181). PSA was not demonstrated in the other components of teratoma, but other glandular components in immature teratoma immunostain with antibody against prostatic acid phosphatase. The presence of prostatic tissue has been occasionally reported in mature cystic teratoma of the ovary (195).

Histologically, immature teratoma uncomplicated by obvious malignant germ cell tumor or carcinoma shows tissue derived from all three germinal layers in various stages of maturation, from embryonic to fetal. Immature tissue includes epithelia of ectodermal and entodermal derivatives, bone, cartilage, and muscle (fig. 3-182).

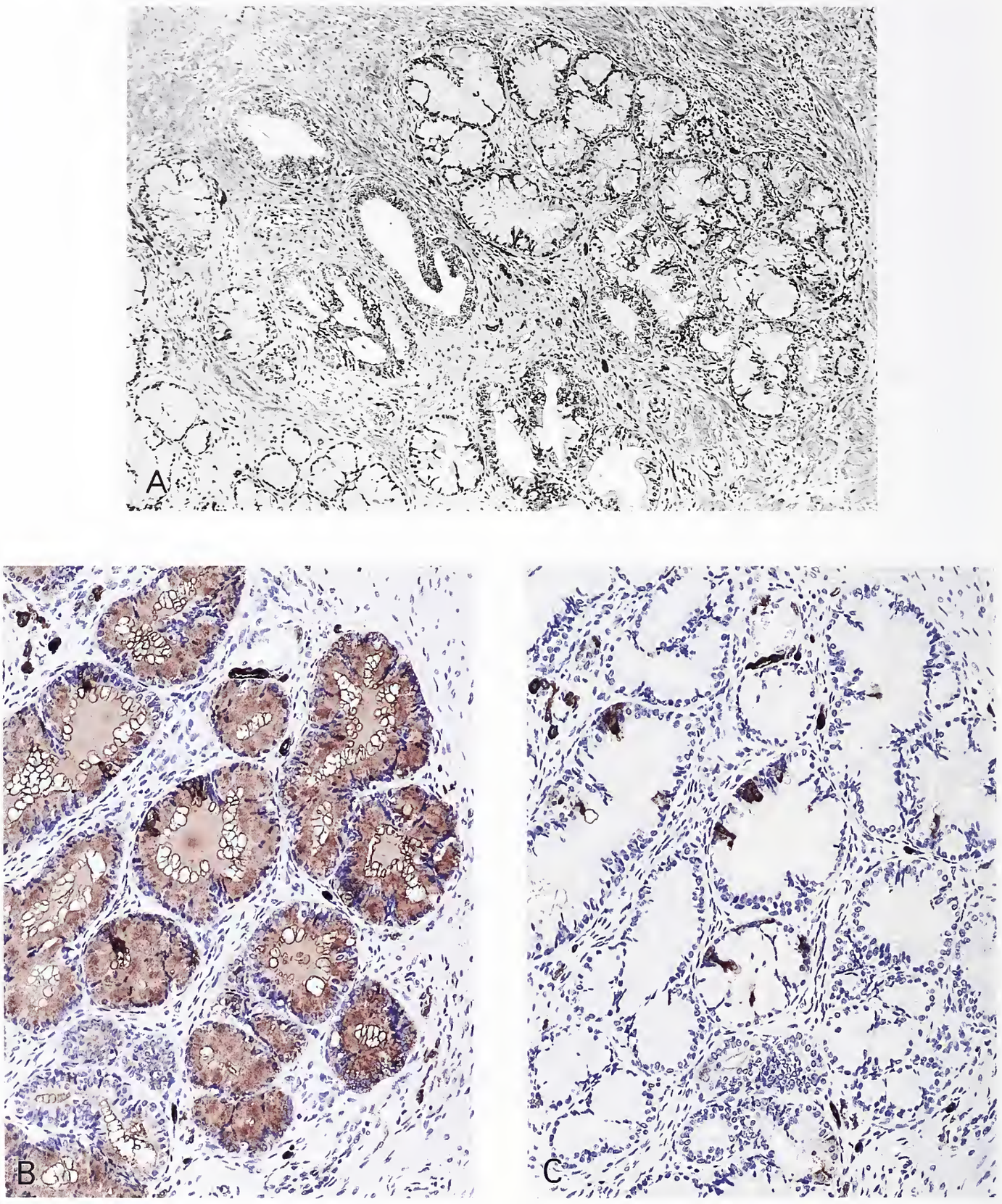


Figure 3-181
MATURE TERATOMA

A: Glandular tissue with interposing smooth muscle cells suggest differentiation toward prostatic tissue, although basal cells are inconspicuous and some cells produce epithelial mucin. Scattered deeply stained cells in the smooth muscle are melanocytes.

B: The glandular cells are strongly positive for prostatic acid phosphatase. Melanocytes are also scattered.

C: However, a few cells are positive for prostate-specific antigen.

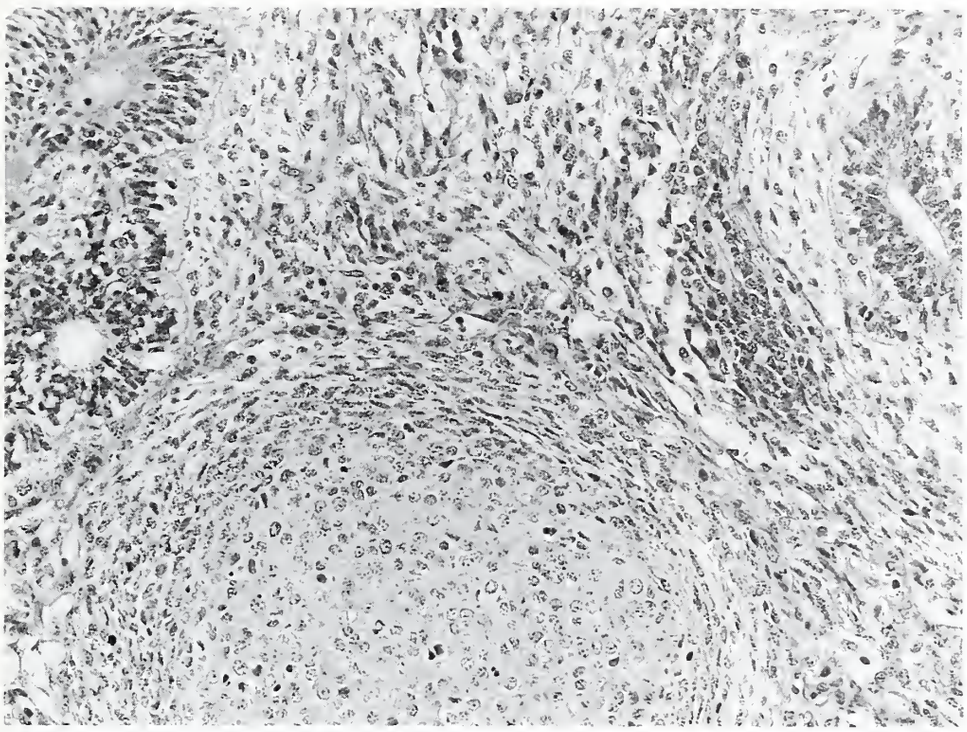


Figure 3-182
IMMATURE TERATOMA
Glands are lined by tall columnar cells with irregularly dispersed nuclei. A single lobule of immature cartilage is evident. Tissue between glands and cartilage consists of active-appearing spindle-shaped cells. However, there is no evidence of malignancy.

Figure 3-183
IMMATURE TERATOMA
Immature neural tissue with neuroepithelium-forming tubules, some of which contain melanin pigment. Spindle-shaped supporting cells are also immature but show no nuclear atypia.

However, in many immature teratomas, neural tissue occupies large areas, and consists of not only glial elements but also neuroepithelium with tubules, rosettes, and retinal anlage (fig. 3-183). Thurlbeck and Scully (206) graded immature teratoma of the ovary according to the amount of immature tissue present, particularly neuroepithelium, and the degree of differentiation, and found the grade to have prognostic value. However, no such study has been conducted for mediastinal teratoma. In our experience, three patients with immature teratoma, in whom the tumor consisted of large areas of mature tissues and small amounts of immature somatic tissues (mature teratoma, benign, grade 1 of Gonzalez-Crussi classification) (Table 3-12),

were alive and well after surgical resection of the tumor. A 37-year-old male with a 10 x 12 cm solid tumor, which consisted of abundant immature neuroectodermal and epithelial tissues and a small amount of mature tissue (grade 3), died of metastasis to the lung 15 months after surgery. The metastatic immature teratoma contained microscopic foci of solid embryonal carcinoma and malignant nongerm cell tumor (fig. 3-184). In seven other patients, immature teratoma was complicated by malignant germ cell and nongerm cell tumors (Table 3-13).

As in the ovary, malignant transformation of mature cystic teratoma (dermoid) occurs in the mediastinum, with features of either squamous cell carcinoma, adenocarcinoma, or poorly differentiated carcinoma (197,202). Germinoma, embryonal carcinoma, yolk sac tumor, and choriocarcinoma have been found in the mediastinum in pure form or in combination with each other and with immature teratoma. Indeed, the presence of a microscopic focus of malignant germ cell tumor in an immature teratoma suggests malignant transformation, and this appears to occur frequently (figs. 3-184, 3-185, 3-187).

Germinoma (Seminoma, Dysgerminoma). Mediastinal germinomas are rare mediastinal tumors, occurring in the second, third, and fourth decades in male patients and rarely in females. In the past, this entity was diagnosed erroneously as seminomatous thymoma. Patients with mediastinal germinoma may be asymptomatic, and the tumor may be found roentgenologically as a large anterior mediastinal mass (see fig. 3-170); alternatively, patients present with nonspecific symptoms and signs of mediastinal tumor including superior vena cava syndrome and cervical lymphadenopathy. However, to establish a diagnosis of mediastinal germinoma, it is necessary to exclude the presence of a primary tumor in the testis or retroperitoneum, at least clinically.

Grossly, the tumor is large, soft, and well circumscribed, and its cut surface is usually homogeneous; large tumors show foci of hemorrhage and coagulation necrosis. Microscopically, the tumor is made up of sheets of large polygonal cells with a distinct cell membrane, clear or finely granular cytoplasm, and centrally located round nuclei with prominent nucleoli; this is supported by a loose stroma densely infiltrated by lymphocytes (see fig. 3-172). The tumor cell cytoplasm contains glycogen. Isolated giant tumor cells resembling syncytiotrophoblasts, like those in testicular seminoma, may also be present. Individual cell necrosis or foci of coagulation necrosis provokes a granulomatous reaction, which may resemble a sarcoid reaction. No cases of spermatocytic or anaplastic seminoma arising in the mediastinum have been reported (194).

Differential diagnosis includes lymphoepithelioma-like carcinoma of the thymus and diffuse large cell lymphoma with sclerosis of the anterior mediastinum. Although hematoxylin and eosin–stained sections are sufficient for establishing a diagnosis in most cases, immunohistochemistry is helpful in difficult cases. Germinoma (seminoma) cells are negative for cytokeratin and epithelial membrane antigen (EMA) and positive for placental alkaline phosphatase (fig. 3-186). Cytokeratin distinguishes germinomas from nonseminomatous germ cell tumors, although 6 of 50 gonadal germinomas showed focal or diffuse cytokeratin reactivity (201). Giant tumor cells resembling syncytiotrophoblasts are positive for beta-hCG. In contrast, lymphoepithelioma-like undifferentiated carcinoma of the thymus is EMA positive and placental alkaline phosphatase negative; diffuse large cell lymphomas are, of course, positive for leukocyte common antigen and frequently show a B-cell phenotype.

Germinoma is highly sensitive to radiotherapy, and therefore, not only total surgical removal of the tumor but also incomplete removal are followed by radiotherapy to the chest, neck, and at times retroperitoneum and other areas; this often cures the disease (189,203). Kersh et al. (191) reported a 100 percent actuarial 5-year survival in patients with mediastinal seminoma. Since germinoma may spread not only to the lungs and lymph nodes but also to extrathoracic organs systemically, combined intensive chemotherapy is indicated.

Embryonal Carcinoma. Embryonal carcinoma is an extremely rare, highly malignant, anterior mediastinal tumor, which may be found as a pure form or in association with other malignant germ cell tumors. When diagnosed, it is often large and invasive to the surrounding organs or structures, and is inoperable or treated by mass-reduction surgery. An elevated level of

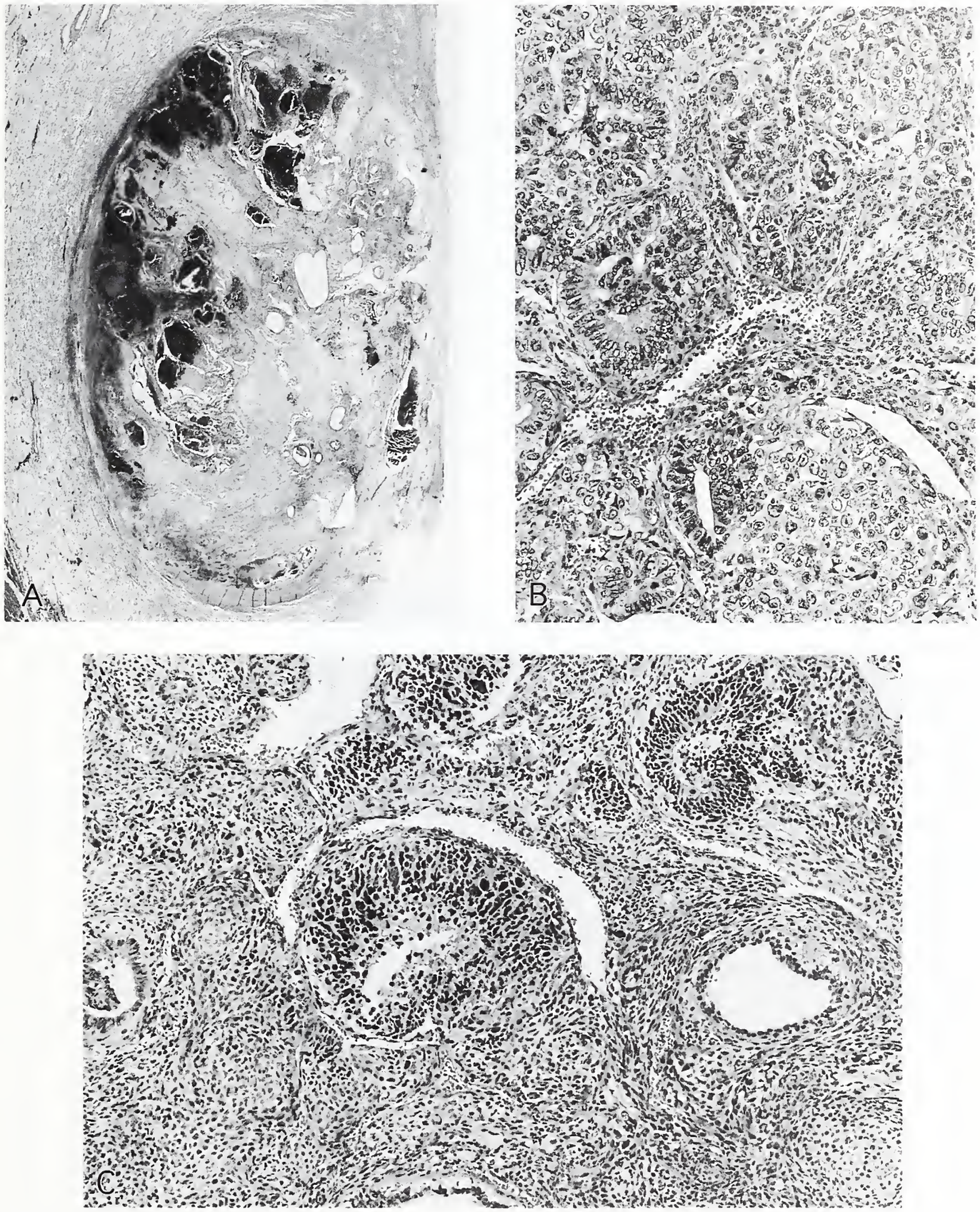


Figure 3-184

MALIGNANT IMMATURE TERATOMA WITH NONGERM CELL COMPONENTS

The primary tumor consisted largely of immature teratoma. However, a tumor metastatic to the lung (A) contains adenocarcinoma and largely solid carcinoma, suggesting embryonal carcinoma in some areas (B), and microscopic foci of what appears to be neuroblastoma in others (C), within the predominantly immature teratoma.

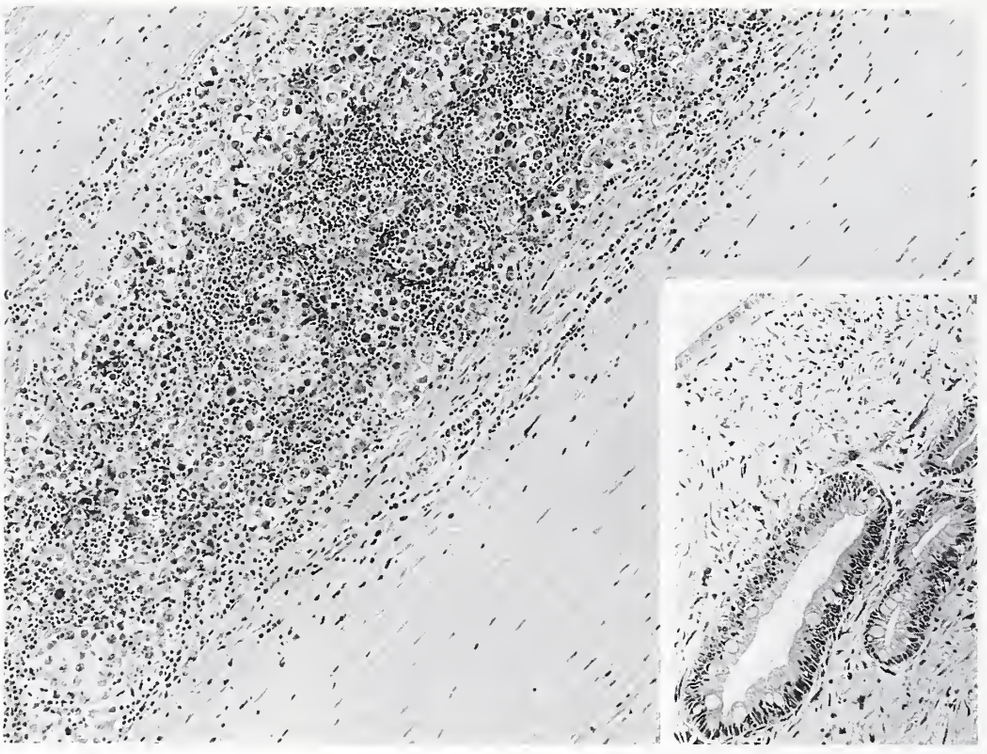


Figure 3-185
SMALL GERMINOMA (SEMINOMA) IN THE WALL OF A MATURE CYSTIC TERATOMA

Solid tumor cell nests are surrounded by stroma densely infiltrated by lymphocytes, which are present in the fibrous wall of multiloculated cysts of mature teratoma. Inset: Mature glandular structures in the remaining portion of the tumor.

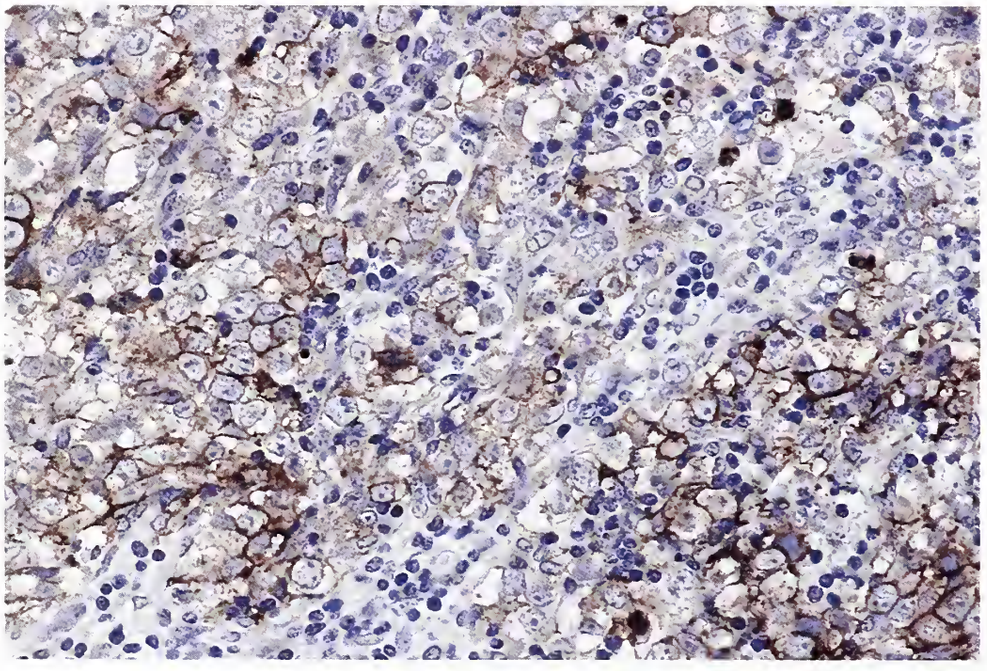


Figure 3-186
GERMINOMA

The cell membrane and cytoplasm of most tumor cells show various degrees of staining for placental alkaline phosphatase. (Immunostaining for placental alkaline phosphatase)

serum alpha-1 fetoprotein (AFP) is diagnostic for either embryonal carcinoma or yolk sac tumor. Cases showing the clinical and chromosomal abnormalities of Klinefelter's syndrome have been reported (192,196).

Grossly, the cut surface is largely occupied by areas of coagulation necrosis and hemorrhage. Histologically, the tumor is composed of sheets, tubules, and papillary structures of large polygonal cells which have round to oval nuclei, prominent nucleoli, often pale-stained cytoplasm, and indistinct cell borders. Mitotic figures are frequent. Immunohistochemically, embryonal carcinomas are frequently positive for placental alkaline phosphatase and cytokeratin, and about one third of the cases are positive for AFP (201). The presence of AFP excludes the possibility of metastatic adenocarcinoma. As in germinoma,

multinucleated giant tumor cells of the syncytiotrophoblastic type may be intermixed; these are positive immunohistochemically for beta-hCG. Absence of Schiller-Duval bodies and a reticular pattern allows differentiation from yolk sac tumor.

Treatment and prognosis are described separately.

Yolk Sac Tumor (Endodermal Sinus Tumor). Although yolk sac tumor is a rare tumor in the mediastinum, it is the most frequent malignant germ cell tumor treated at our institution. The majority of patients are males in their twenties and thirties (198,204,208). Of 76 cases collected by Marchevsky and Kaneko (194), only 1 occurred in a female patient (187). Two of six children with mediastinal yolk sac tumor reported by Hawkins et al. (188) were girls aged 2 and 10 years.

Yolk sac tumor is highly malignant, and often large and invasive when detected. The serum level of AFP is markedly elevated. The tumor occurs as a pure form or in combination with immature teratoma or other forms of malignant germ cell tumor (figs. 3-173, 3-187, 3-188).

Histologically, the tumor cells grow diffusely, forming tubular and papillary structures. Characteristic and diagnostic features are a reticular pattern with various-sized spaces lined by flattened cells and the presence of Schiller-Duval bodies, which are papillae composed of a central vessel covered by columnar tumor cells (fig 3-187, bottom). According to Ulbright et al. (210), many yolk sac tumors form hepatic-like foci (22 percent), enteric-like glands (34 percent), and parietal yolk sac structures (92 percent). The last is characterized by the intercellular accumulation of basement membrane substance in generally thick and longitudinally arranged bands of eosinophilic material. Eosinophilic hyaline droplets may be seen within and outside the cells, which are PAS-positive and may contain immunoreactive AFP (fig. 3-188). Yolk sac tumor also contains immunoreactive alpha-1-antitrypsin and cytokeratin. Placental alkaline phosphatase is present in about half the cases and carcinoembryonic antigen in 11 percent (201).

Prognosis is poor, unless the tumor is completely excised surgically or responds to intensive chemotherapy combined with adjuvant radiotherapy and surgery. Patients with advanced stage tumors often take a rapid downhill course with metastasis to the lung, liver, brain, or bone.

Choriocarcinoma. This is also a rare malignant tumor arising in the anterior mediastinum, which develops in young adults of both sexes. Gynecomastia is a frequent finding, and an elevated serum level of beta-hCG is diagnostic.

Grossly, the tumor is characteristically hemorrhagic. Microscopically, it consists of mononuclear cytotrophoblastic cells and giant syncytiotrophoblastic cells, frequently bordering extensive areas of hemorrhage. Choriocarcinoma is seen as a pure form or in combination with immature teratoma or other forms of germ cell tumor such as embryonal carcinoma. Immunohistochemically, beta-hCG is positive in syncytiotrophoblastic cells and some cytotrophoblastic cells (fig. 3-190). In addition, cytokeratin is positive in all cases and placental alkaline phosphatase and epithelial membrane antigen in about half (201).

In the past, patients with this tumor invariably died due to hematogenous spread to the lung, liver, brain, or bone. Recently, however, the tumor has been successfully treated with a chemotherapeutic protocol of cisplatin and etoposide, with or without bleomycin. The effectiveness of the treatment can be monitored using chest X-ray films (fig. 3-189) and the serum level of beta-hCG. Since metastatic tumors in the lung are also extensively hemorrhagic, abnormal densities remain even after this serum marker has been reduced to a normal level. Surgical removal of multiple lung lesions following the return of the marker to a normal serum level discloses hemorrhagic and necrotic tissue surrounded by granulation tissue in most nodules, and tumor cell ghosts may show beta-hCG immunoreactivity. However, there may be microscopic foci of remnant or regrowing tumor cells at the borders of the nodules (fig. 3-190B). Therefore, the timing of chemotherapy discontinuation is important, and at present surgery is recommended even after effective chemotherapy.

Malignant Teratoma with Nongerminal Malignant Tumor. Multiple sections of immature teratoma occasionally disclose microscopic foci of nongerm cell malignant tumors, such as adenocarcinoma, undifferentiated carcinoma, or sarcoma (figs. 3-184, 3-191). However, germ cell tumors in which nongerminal malignancy predominates are rare. These malignant tumors are believed to arise within teratomatous foci. A

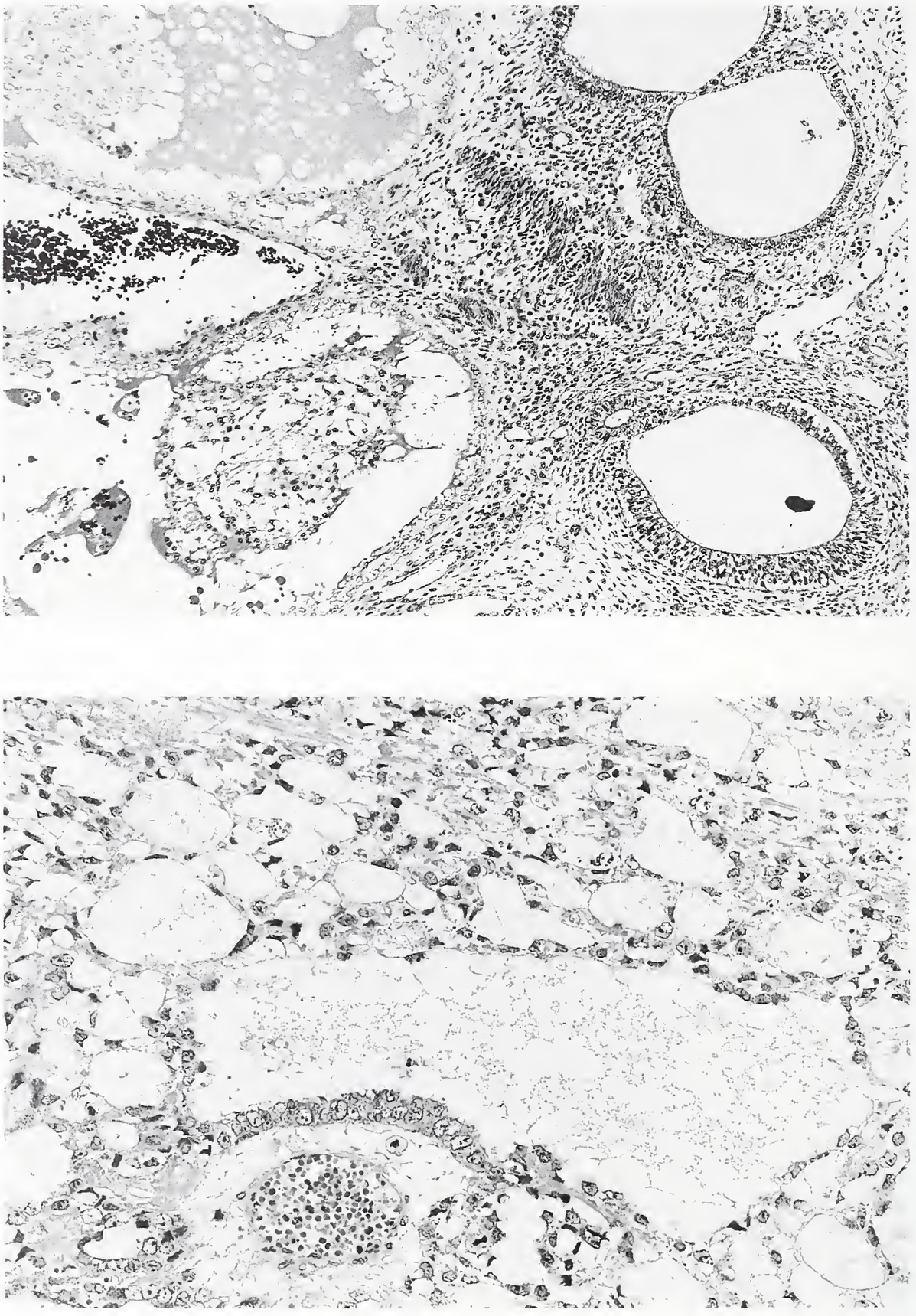


Figure 3-187
SMALL YOLK SAC TUMOR IN IMMATURE TERATOMA

Top: Within this immature teratoma containing glands and smooth muscle cells, there is a microscopic focus of a tumor showing a reticular pattern.

Bottom: In another area there is a typical yolk sac tumor with a reticular pattern and an incomplete Schiller-Duval body.

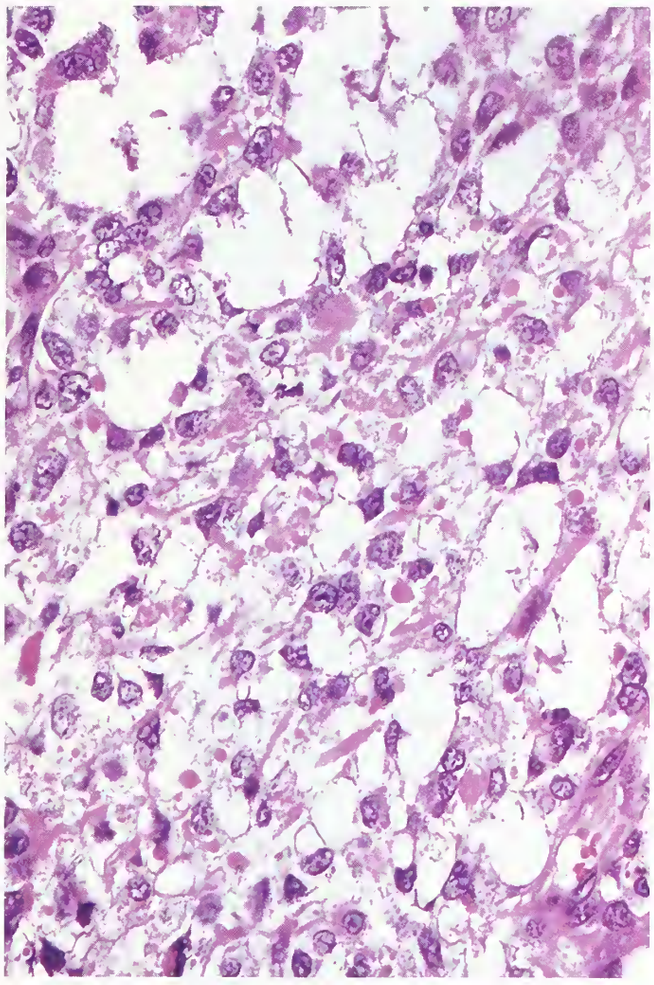


Figure 3-188
YOLK SAC TUMOR
In the area showing a reticular pattern, eosinophilic hyaline droplets are evident both within and outside the cell.

variety of malignant tumors have been described: embryonal rhabdomyosarcoma, angiosarcoma, myxoid liposarcoma, chondrosarcoma, leiomyosarcoma, glioblastoma multiforme, neuroblastoma, nephroblastoma, adenosquamous carcinoma, and more, either in a pure form or in combination (193,209). The occurrence of carcinoma in teratoma is much less frequent than mesenchymal tumor and is extremely rare (185, 197). Some components may remain after complete disappearance of the germ cell tumor following intensive chemotherapy; remnants are considered the result of selective action of chemotherapy. Therefore, chemotherapy protocols may need to be altered to include sarcoma-oriented drugs for this particular group of patients, although the role of other forms of chemotherapy remains unclear (193,209).

Treatment and Prognosis. Mature teratoma is a benign tumor, but it may enlarge excessively and compress and displace neighboring thoracic organs, or become malignant (185, 197). Immature teratoma is often large when diagnosed, and may adhere to or invade adjacent structures; it is frequently combined with malignant germ cell tumor (Table 3-13). Therefore, surgical removal is indicated whenever possible. Encapsulated immature teratoma in infants and children younger than 15 years old seems to behave like mature teratoma (194). When immature teratoma is combined with malignant germ cell tumor, growth is aggressive; frequently, only biopsy or reduction surgery can be performed, followed by radiotherapy and chemotherapy with poor results. However, aggressive chemotherapy combined with radiotherapy and surgery may achieve cure in some patients.

Mediastinal germinomas (seminomas) are highly curable and radiotherapy for mediastinal disease or cisplatin-based chemotherapy for metastatic disease results in long-term survival in 80 percent or more of patients (199).

Mediastinal nonseminomatous malignant germ cell tumors were invariably fatal until a decade ago. They are a clinically and biologically distinct subset of germ cell neoplasms, and have a poor prognosis, with the worst survival among patients with gonadal and extragonadal germ cell tumors (199,207). Intensive chemotherapy using cisplatin, vinblastine, etoposide, and bleomycin for gonadal germ cell tumors is effective for extragonadal germ cell tumors including nonseminomatous malignant mediastinal germ cell tumors (figs. 3-189, 3-190, 3-192), and an increasing incidence of successful cure has been reported (Table 3-13) (183,188,204). Poor-risk patients with extragonadal nonseminomatous germ cell tumors may be treated with high-dose etoposide and carboplatin followed by autologous bone marrow transplantation (200). The patient with an "entirely necrotic tumor" shown in Table 3-13 was treated similarly, and is currently alive after more than 3 years without evidence of disease (181a). Tumors remaining after such intensive treatment often show marked pleomorphism with frequent giant tumor cells (fig. 3-193), which may mimic the histology of choriocarcinoma. Therefore, immunohistochemistry should be done to establish a final diagnosis.

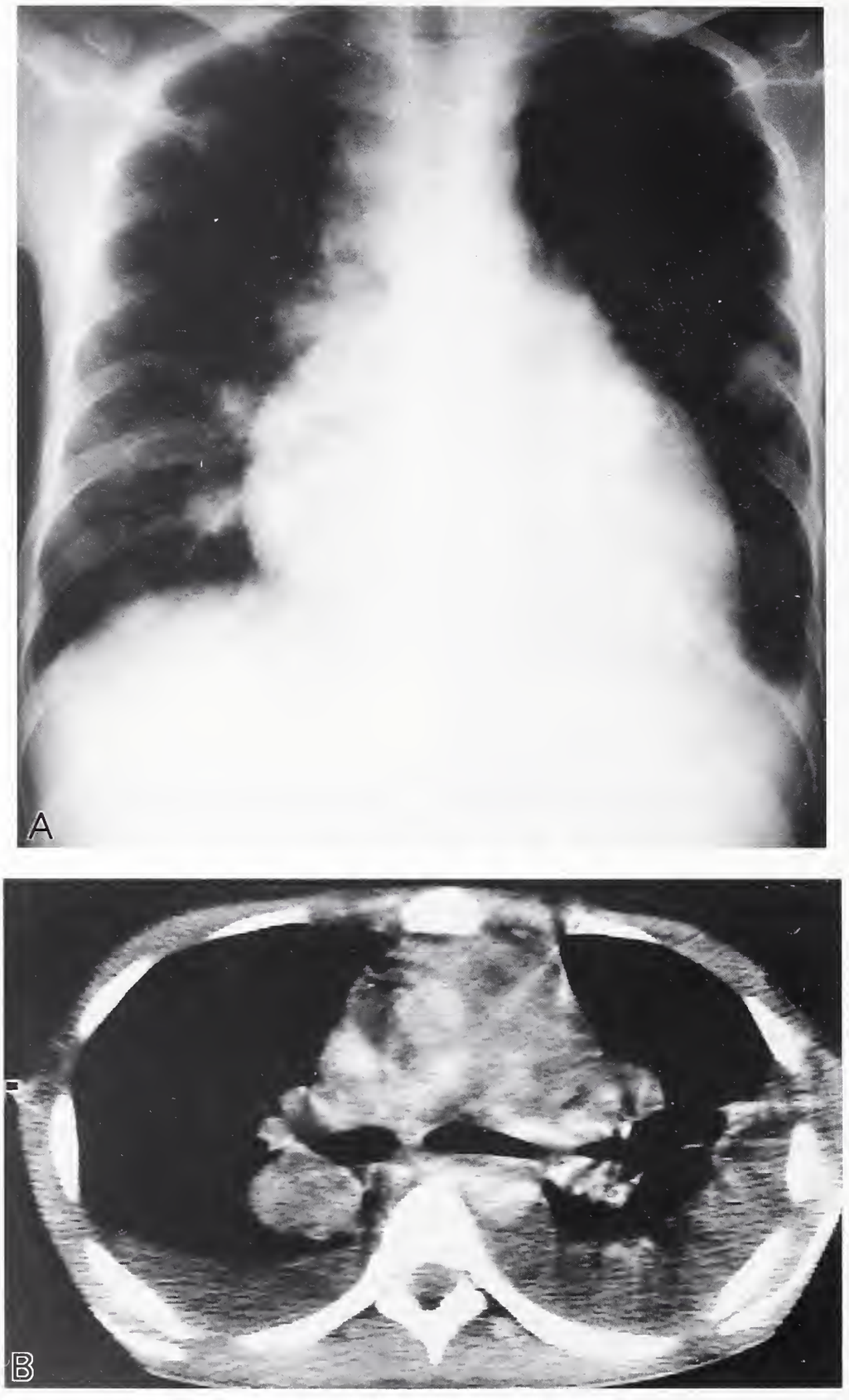


Figure 3-189
CHORIOCARCINOMA AFTER TREATMENT WITH ANTITUMOR AGENTS

A: Prior to chemotherapy, plain chest roentgenogram shows widening of the mediastinal density, multiple metastases up to 3 cm in diameter in the lung field, enlargement of cardiac density due to pericardial effusion, and bilateral pleural effusion.

B: CT at the level of the tracheal bifurcation shows anterior mediastinal tumorous densities associated with the metastatic tumor in the lung and bilateral pleural effusion.

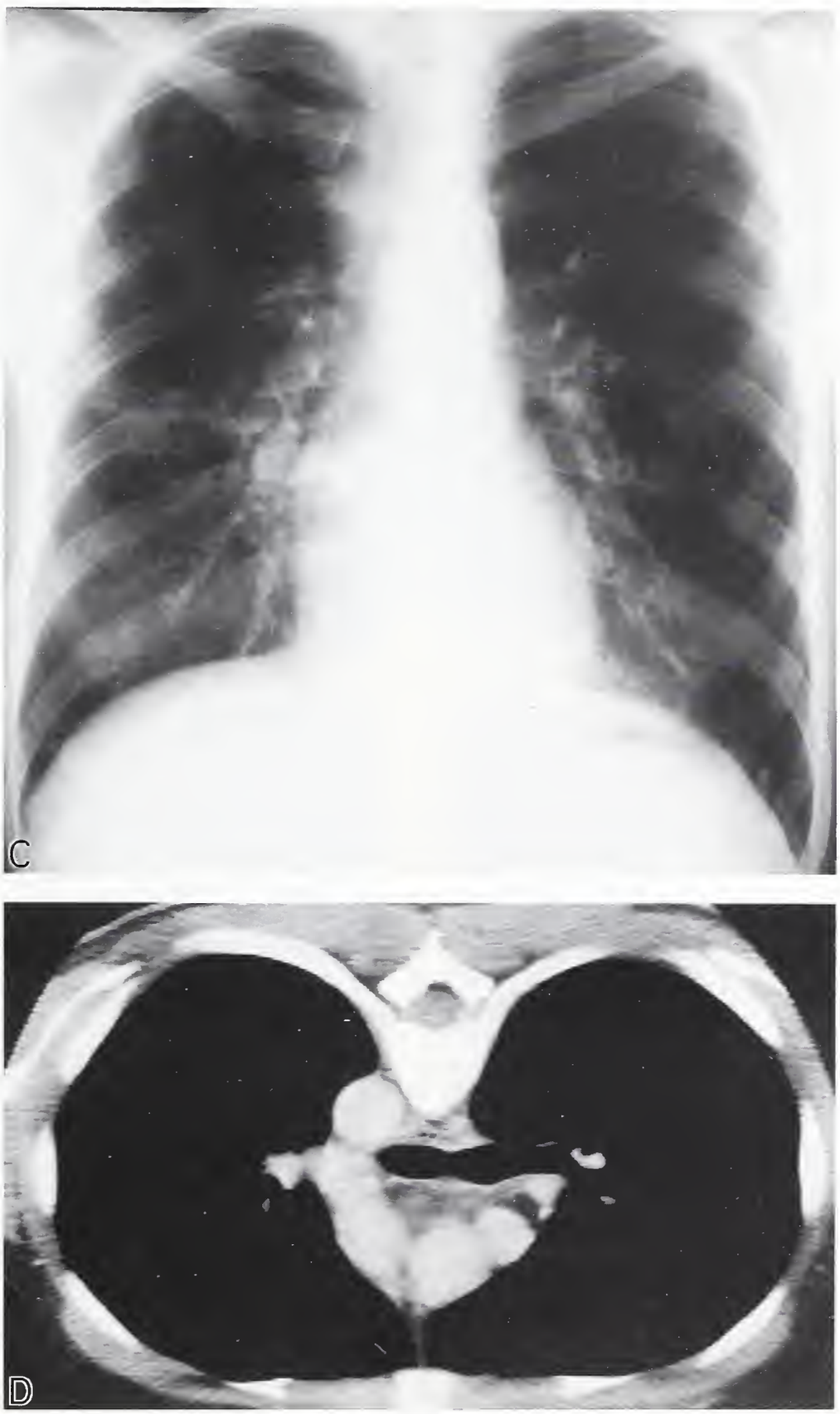


Figure 3-189 (Continued)

C: After chemotherapy, a plain chest X-ray film reveals minimal widening of the superior mediastinum and disappearance of the nodular tumorous densities in the lung field and the pleural effusion, leaving only reticular densities in both lower lobes.

D: CT at the level of the tracheal bifurcation discloses some enlargement of the pretracheal lymph nodes and almost complete disappearance of the mediastinal tumor, lung metastasis, and pleural effusion (same case as that in figure 3-178).

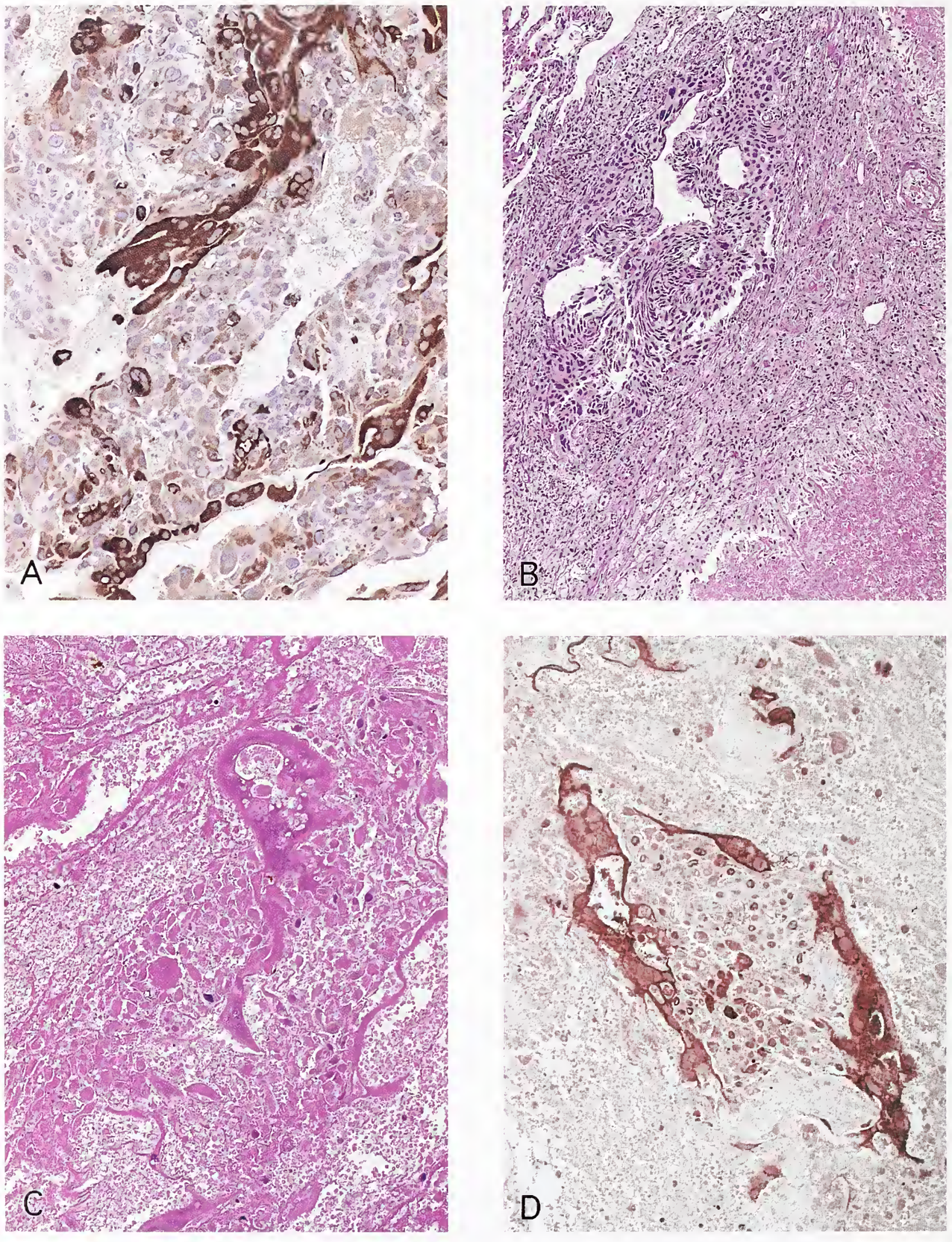


Figure 3-190
CHORIOCARCINOMA AFTER TREATMENT WITH ANTITUMOR AGENTS

A: Untreated mediastinal choriocarcinoma shown in figure 3-174 is stained for beta-hCG as a control.

B: Several lung metastases removed surgically were almost entirely necrotic, and apparently viable tumor tissue remained in only one nodule between the lung tissue and granulation tissue bordering necrotic tissue.

C: Within the necrotic tissue, ghosts of cytotrophoblasts and syncytiotrophoblasts can be identified.

D: These show intense reactivity upon immunostaining with anti-beta-hCG (same case as that in figures 3-178, 3-189).

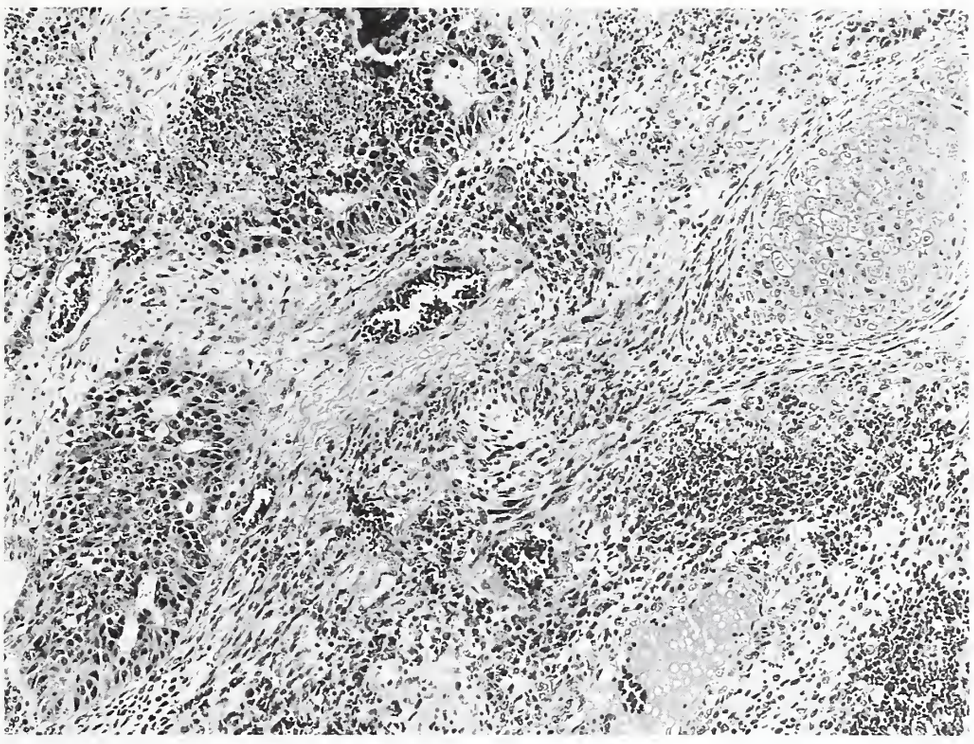


Figure 3-191
MALIGNANT TERATOMA WITH NONGERMINAL MALIGNANT TUMOR
Within this immature teratoma with a mesenchymal component are several nests of moderately differentiated adenocarcinoma.

MALIGNANT LYMPHOMA

Malignant lymphoma of the mediastinum may be primary in this location or secondary to generalized disease. In order of frequency, it manifests as an anterior, superior, or middle mediastinum mass (232). All major types of malignant lymphoma can involve the mediastinum. A general description of the clinicopathologic features of various malignant lymphomas can be obtained in the second series Armed Forces Institute of Pathology (AFIP) Fascicle on the hematopoietic system, or other major textbooks of hematopathology (222,225,237b). Discussion in this chapter is confined to malignant lymphomas that present as primary neoplasms in the mediastinum, since these can be difficult to distinguish from thymoma. Clinically, most malignant lymphomas of the mediastinum affect individuals younger than those with thymoma, demonstrating different growth patterns and more rapid rates of dissemination. The response of malignant lymphoma to chemotherapy and radiation therapy is generally better than that of thymoma.

Hodgkin's Disease

Hodgkin's disease in the mediastinum may involve thymus, mediastinal lymph nodes, or both. Of four major histologic subtypes, the nodular sclerosis type is by far the most common. Most patients are young female adults. Clinical symptoms related to local pressure (dyspnea, cough, or chest pain) may be present. However, Hodgkin's disease is often detected by routine chest X ray, appearing as an anterior-superior mediastinal mass in asymptomatic patients (233).

A diagnosis of nodular sclerosis may be suspected at the time of macroscopic examination by the delineation of distinct nodules defined by retracted grayish white interconnecting bands on the cut surface (fig. 3-194). When nodular sclerosis Hodgkin's disease involves the thymus, the tumor is sharply outlined and sometimes surrounded by a thick capsule. Unlike thymoma, the nodules may be multiple and residual thymic remnants may be present (213).

Histologically, nodular sclerosis is characterized by orderly bands of interconnecting collagenous connective tissue that partially or entirely subdivide abnormal lymphoid tissue into isolated cellular nodules (fig. 3-195). In some cases, the entire lesion may undergo spontaneous sclerosis, while at the opposite extreme, the lesion may be predominantly cellular, with the formation of bands and isolation of nodules limited to only a small portion of the tumor.

The cellular proliferation within the nodules is polymorphic, with small and large lymphocytes,

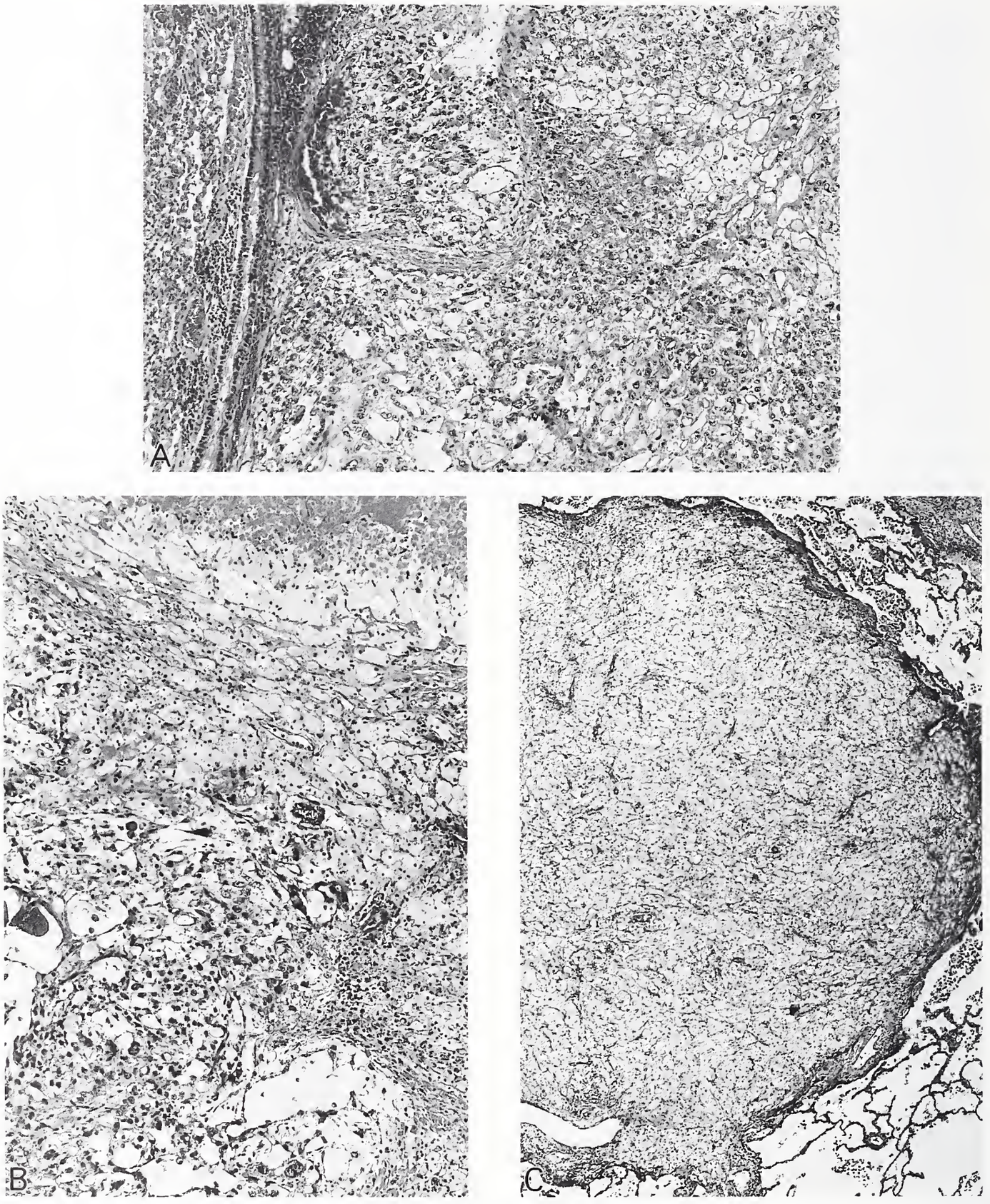


Figure 3-192
YOLK SAC TUMOR AFTER TREATMENT WITH ANTITUMOR AGENTS

A: A tumor metastatic to the right upper lobe shows only a mild degree of degenerative change.

B: Metastasis in the right lower lobe shows moderate therapeutic effects, as evidenced by large areas of necrosis bordered by foamy histiocytes and cytolytic changes in the remaining tumor cells.

C: Tumor in the left lower lobe has been cured and completely replaced by foamy histiocytes (same case as that in figure 3-173.)

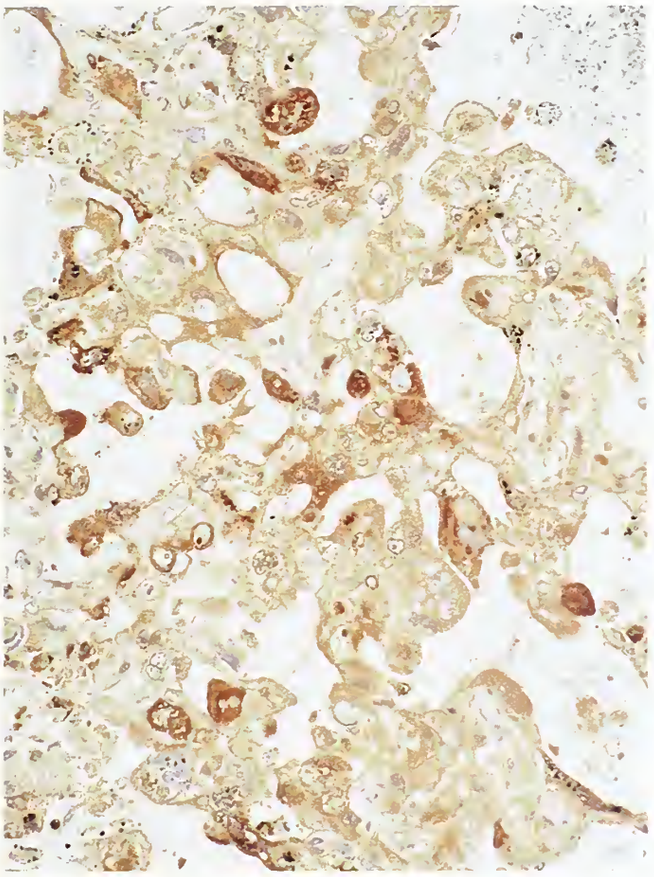


Figure 3-193
YOLK SAC TUMOR AFTER CHEMOTHERAPY
The tumor cells are markedly enlarged and degenerative, and no definite histologic diagnosis was possible from hematoxylin and eosin-stained sections. However, a reticular pattern suggestive of yolk sac tumor was retained, and this was confirmed by immunostaining for alpha-1-fetoprotein.

Figure 3-194
HODGKIN'S DISEASE, NODULAR SCLEROSIS
The distinct nodules on the cut surface of this lymph node strongly suggest the diagnosis.

plasma cells, eosinophils, and histiocytes. The distinctive feature is the presence of Reed-Sternberg cells and their lacunar variants (fig. 3-196) (213). The latter occur in clusters and have abundant water-clear or slightly eosinophilic cytoplasm with sharply defined cellular borders situated in lacuna-like spaces. The lacuna-like spaces are artifacts of formalin fixation and are less obvious in tissues fixed in mercury-containing fixatives such as B5 (213). The nuclei of the lacuna cells are usually hyperlobated with delicate chromatin and small nucleoli.

Variants of nodular sclerosis may occasionally give rise to problems in diagnosis (213). These variants include cellular phases without fibrous bands, and lymphocyte depleted, sarcomatous, and syncytial types. Immunohistochemistry is a great help in these cases. Reed-Sternberg cells and their lacuna variants are reactive with CD15 and CD30 antibodies. The former recognize X-hapten and the latter an activation marker (gp120). Leu-M1 is commonly used for CD15 and BerH2 for CD30 (fig. 3-197). Both antibodies are reactive with antigens in paraffin-embedded tissue. Occasionally, Reed-Sternberg cells and their variants are positive for B-cell marker recognized by CD20 (L26) antibody or T-cell marker by CD45RO (UCHL-1) antibody (fig. 3-198) (213,225). The significance of this finding is not clear since the histogenesis of Hodgkin's disease remains to be understood. Finally, gene rearrangement studies have not shown consistent rearrangements of either immunoglobulin or T-cell receptor genes in Hodgkin's disease.

Hodgkin's disease had been misinterpreted as a form of thymoma ("granulomatous thymoma") because it superficially resembles thymoma due to the interlacing of fibrous bands and polymorphous inflammatory infiltration (233). In addition, thymic epithelial cells can react with a peculiar hyperplastic response to the presence of the lymphoma and resemble the spindle cell

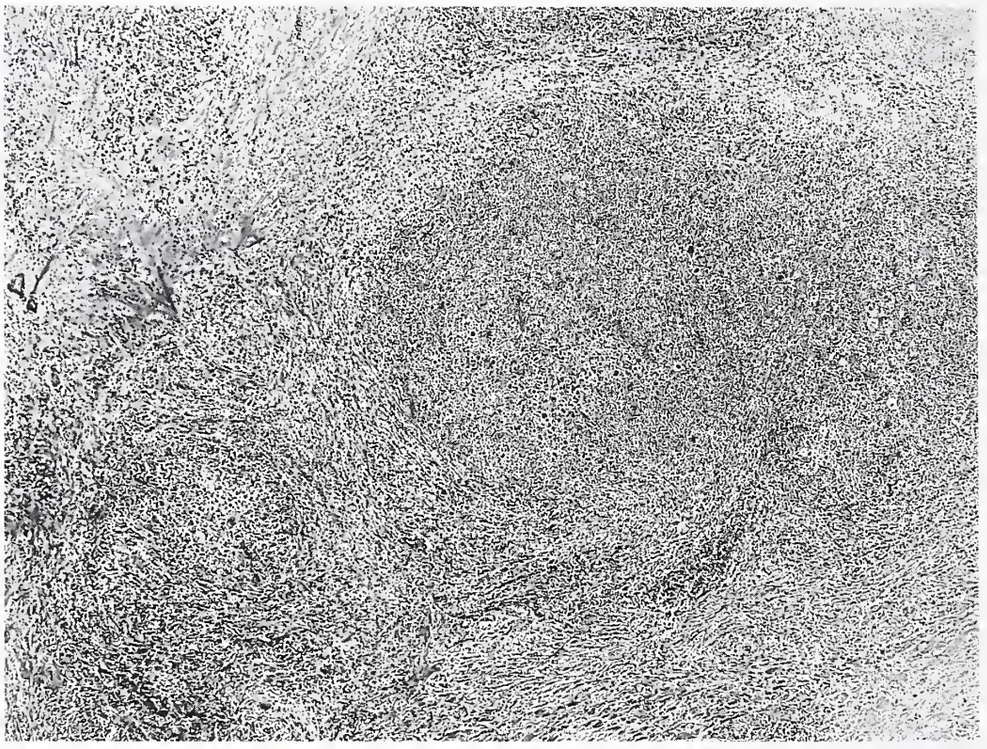


Figure 3-195
HODGKIN'S DISEASE, NODULAR SCLEROSIS
Bands of collagenous tissue subdivide the lymph node into multiple discrete nodules.

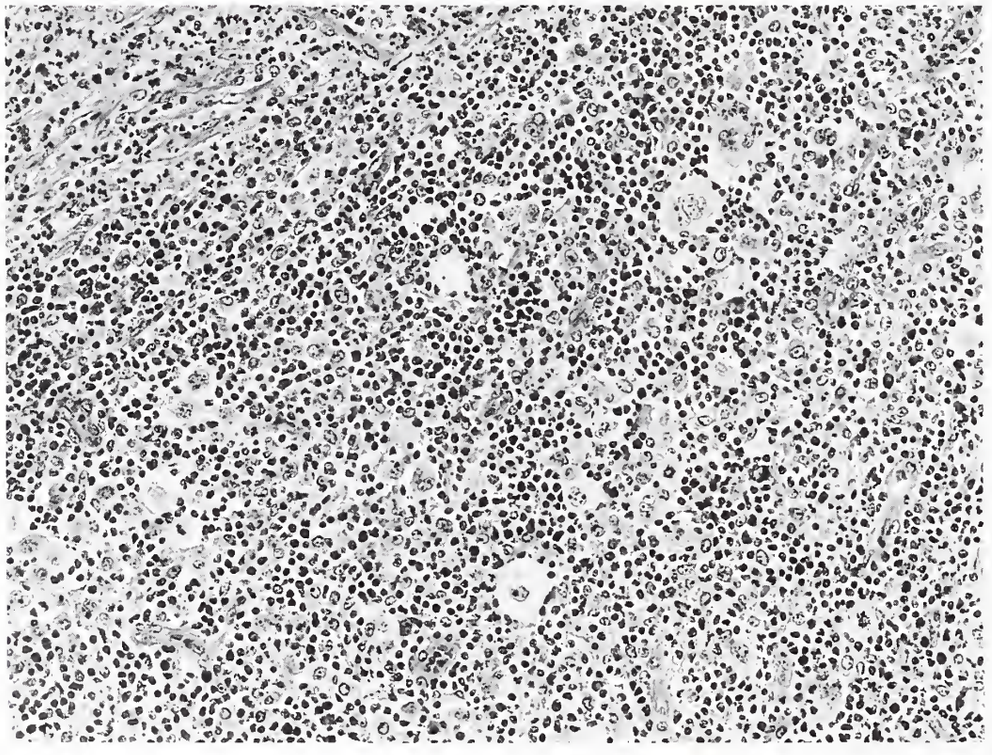


Figure 3-196
LACUNA CELLS WITH ABUNDANT CLEAR CYTOPLASM
Characteristic features are apparent in this formalin-fixed tissue.

proliferation of thymoma (216). However, in Hodgkin's disease fibrous bands are rounded and not angulated as in thymoma; epithelial hyperplasia is not present throughout the tumor; and diagnostic Reed-Sternberg cells or their lacunar variant are identifiable. Immunohistochemistry can clarify the situation.

Another interesting feature frequently associated with Hodgkin's disease is the development of epithelium-lined cysts of various sizes (fig. 3-199) (233). They contain clear fluid or grumous material. This is the result of a peculiar reaction of thymic epithelial cells. Occasionally, the entire lesion has a macroscopic appearance indistinguishable

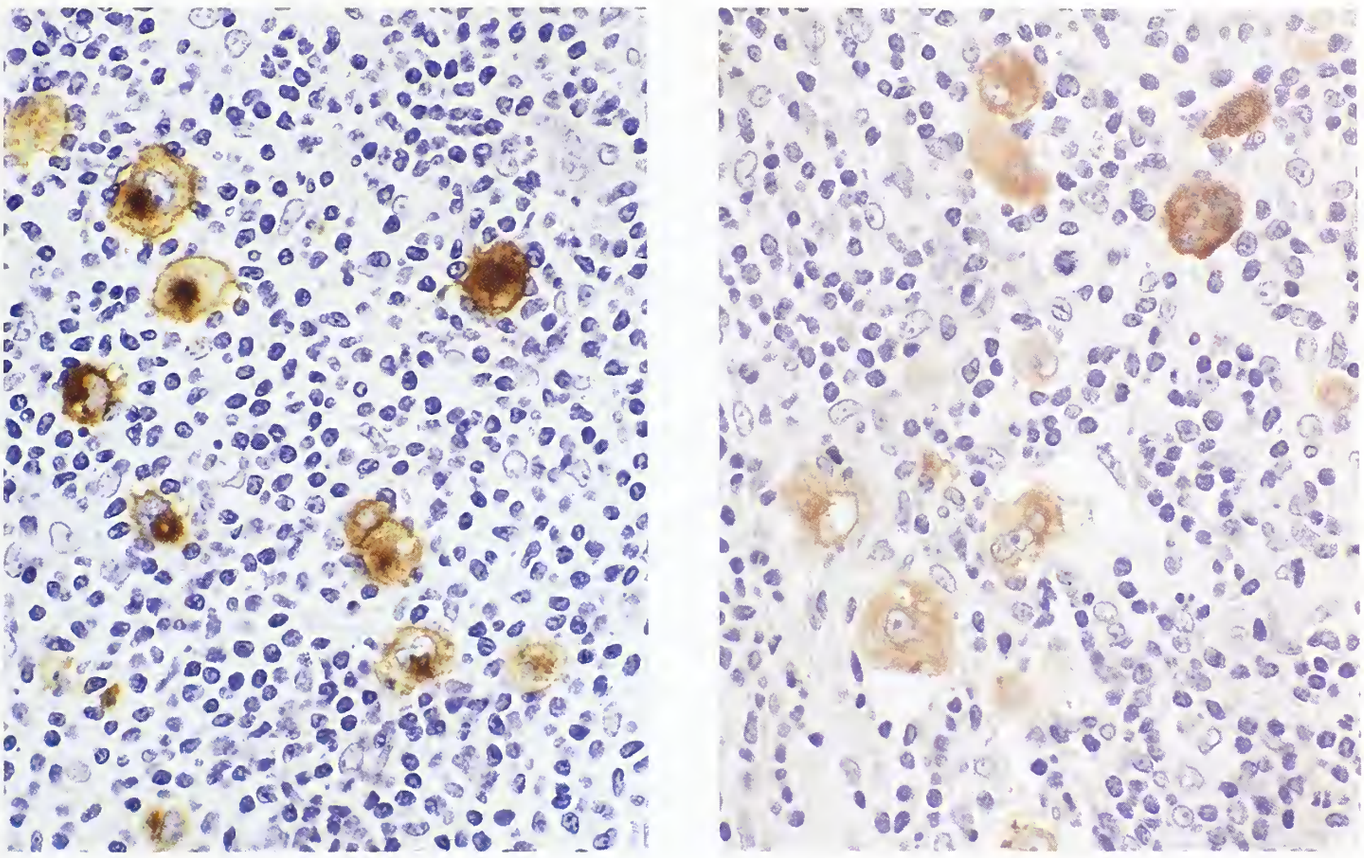


Figure 3-197
IMMUNOHISTOCHEMISTRY OF HODGKIN'S DISEASE BY CD15 (Leu-M1) AND CD30 (BerH2) ANTIBODIES
Left: Cell membrane and Golgi area are strongly positive for CD15.
Right: CD30 demonstrates cytoplasmic staining of lacuna cells.

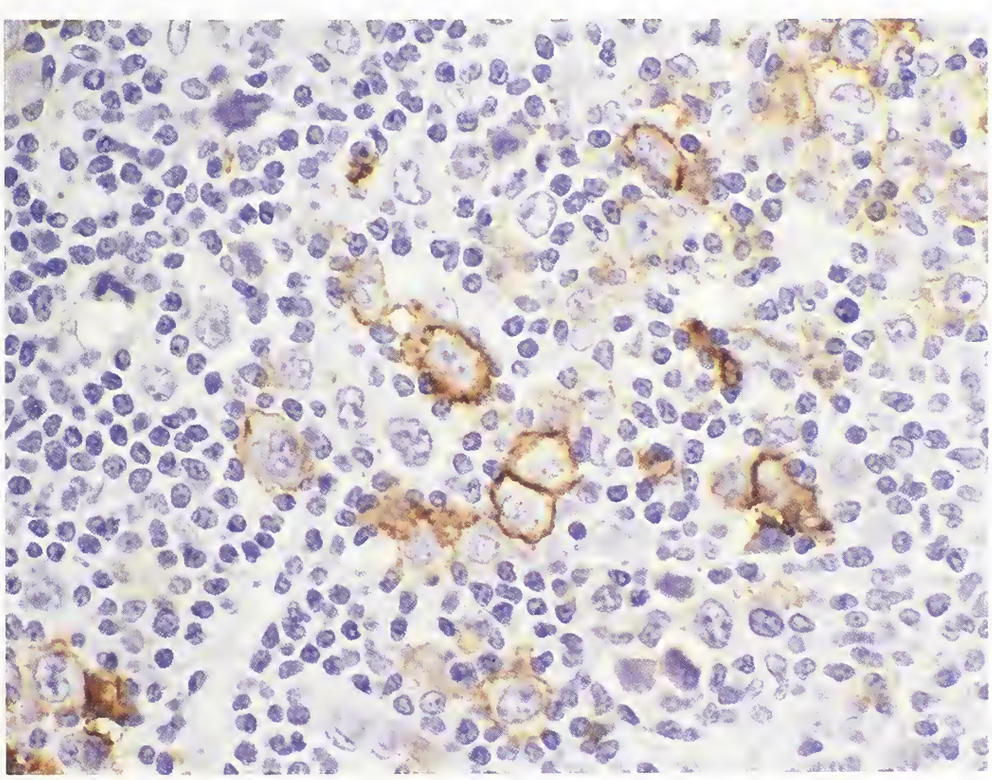


Figure 3-198
STAINING OF LACUNA CELL BY CD20 (L26)
The significance of positive staining is not known.

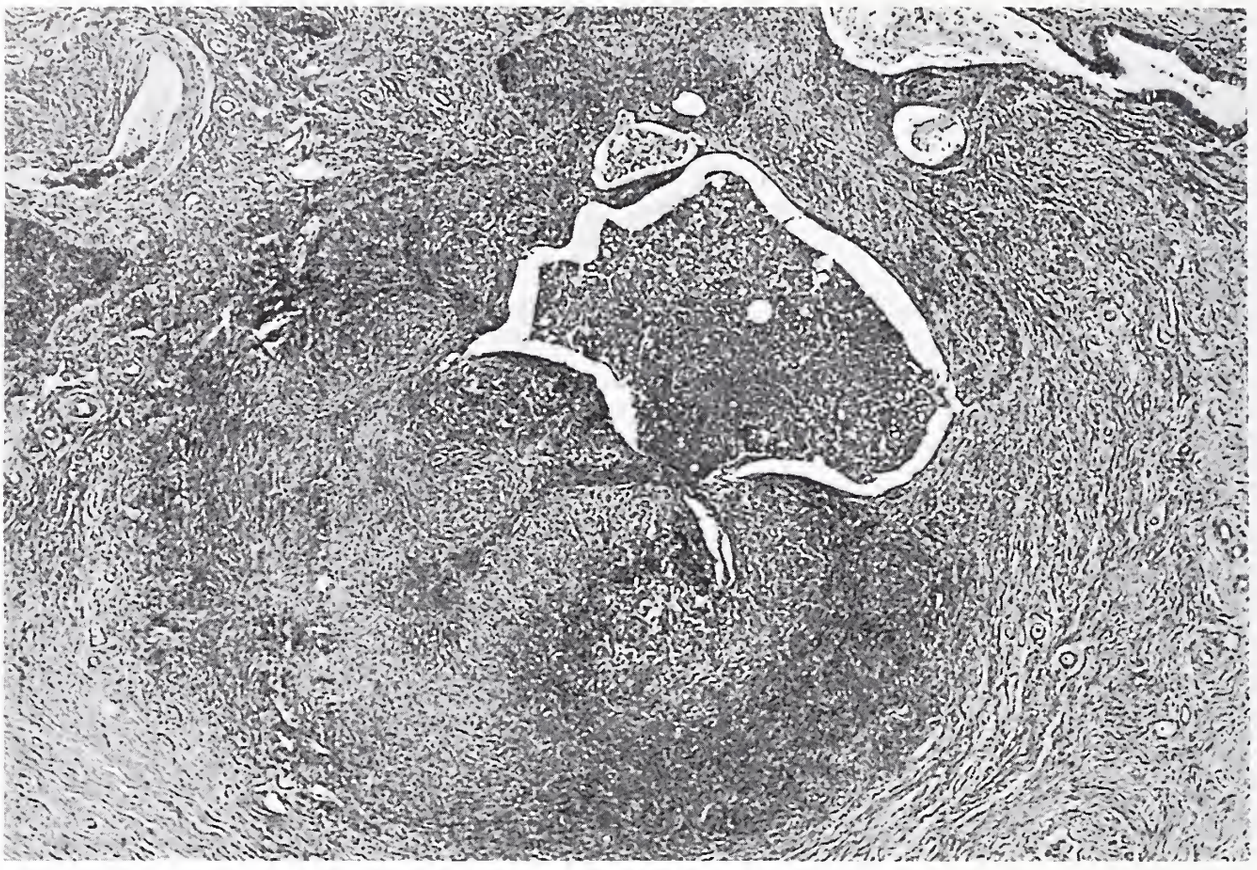


Figure 3-199
HODGKIN'S DISEASE, NODULAR SCLEROSIS

A nodule of thymic Hodgkin's disease is seen in intimate contact with an epithelial-lined cyst. (Fig. 161 from Fascicle 13, 2nd Series.)

from that of benign thymic cysts. The cystic change may be seen in other disorders but is more common in Hodgkin's disease.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma (LBL) is mainly a disease of children and adolescents. It has a peculiar predilection for the thymus. Although 20 percent of LBLs are derived from precursor B cells, most are derived from precursor T cells and express phenotypes corresponding to the various stages of the intrathymic differentiation of these cells (221). LBL and acute lymphoblastic lymphoma (ALL) of precursor T-cell type share overlapping clinical, pathologic, cytogenetic, and molecular features. For this reason, some investigators have suggested that LBL and ALL are simply different manifestations of the same disease. However, unlike ALL, LBL has no or minimal peripheral blood or bone marrow involvement and normal or slightly decreased white blood cell and platelet counts at presentation. Patients with LBL typically present with acute respiratory distress due to a large mediastinal mass (fig. 3-200) (233). Males are affected 2 to 4 times more frequently than females. Shortly after presentation, bone marrow, lymph node, and visceral involvement occur and leukemic spread follows. The central nervous system and gonads are often involved.

Histologically, LBL exhibits a diffuse, infiltrative pattern of growth. The infiltration involves the thymic parenchyma and can be confused with lymphocyte predominant thymoma (fig. 3-201) (221,233). The neoplastic cells of this lymphoma resemble cortical thymocytes in terms of morphology, immunophenotype, and genotype. LBL has been subdivided into convoluted and nonconvoluted subtypes according to the nuclear configuration of the neoplastic cells. The presence of occasional convoluted nuclei qualifies an LBL as the convoluted subtype; about 80 percent of LBLs can be classified as convoluted based on these criteria (221).

Figure 3-200
LYMPHOBLASTIC LYMPHOMA, CONVOLUTED TYPE, OF THE THYMUS
This chest roentgenogram shows a large anterosuperior mediastinal mass. (Fig. 150 from Fascicle 13, 2nd Series.)

The neoplastic cells of convoluted and nonconvoluted LBL share characteristic cytologic features. The cells are medium in size and have scanty cytoplasm, ill-defined cell borders, thin but distinct nuclear membranes, finely dispersed and evenly distributed dust-like chromatin, and inconspicuous nucleoli (fig. 3-202). Nuclei are classified as convoluted when they possess one or more deep clefts or infoldings, resulting in a lobulated appearance. The mitotic index is high; the rapidly proliferating cells expand the thymic lobules, surround persistent Hassall corpuscles, and infiltrate vessel walls, fibrous trabeculae, and the thymic capsule. In the periphery of the tumor, the neoplastic cells often split the collagen fibers and infiltrate between them in a single-file arrangement (fig. 3-203). Confirmation of the histologic diagnosis can be made by the demonstration of terminal deoxynucleotidyl transferase (TdT) and immature immunophenotypes corresponding to different developmental stages of thymocytes. Genetic studies of antigen receptor genes may be helpful if monoclonality is proved by the presence of rearrangements. Recently, a rare case of thymic lymphoblastic lymphoma originating from a thymic precursor committed to natural killer cell differentiation was reported, of which the phenotype and genotype were different from those of thymic T cells (216a).

In adults, LBL should be distinguished from lymphocyte-rich thymoma. This diagnostic dilemma most commonly occurs in small and often fragmented mediastinoscopic biopsies in which the characteristic features of thymoma, such as perivascular spaces, may be absent. Careful observation of the cytologic and histologic manifestations usually prevents diagnostic confusion with lymphocyte predominant thymoma (221). In contrast to neoplastic lymphoblasts, benign thymocytes in thymoma generally contain clumped chromatin and are mitotically inactive. Immunophenotyping is not usually helpful for differential diagnosis because benign thymocytes express immunophenotypes similar to those of neoplastic T lymphoblasts.

Figure 3-201
INVOLVEMENT OF THYMUS BY LYMPHOBLASTIC LYMPHOMA

Adjacent to the thymic tissue, diffuse infiltration of lymphoma cells is seen. A few Hassall corpuscles are trapped in the tumor. (Courtesy of Dr. Koichi Shimizu, Tokyo.) (Figures 3-201 and 3-202 are from the same case.)

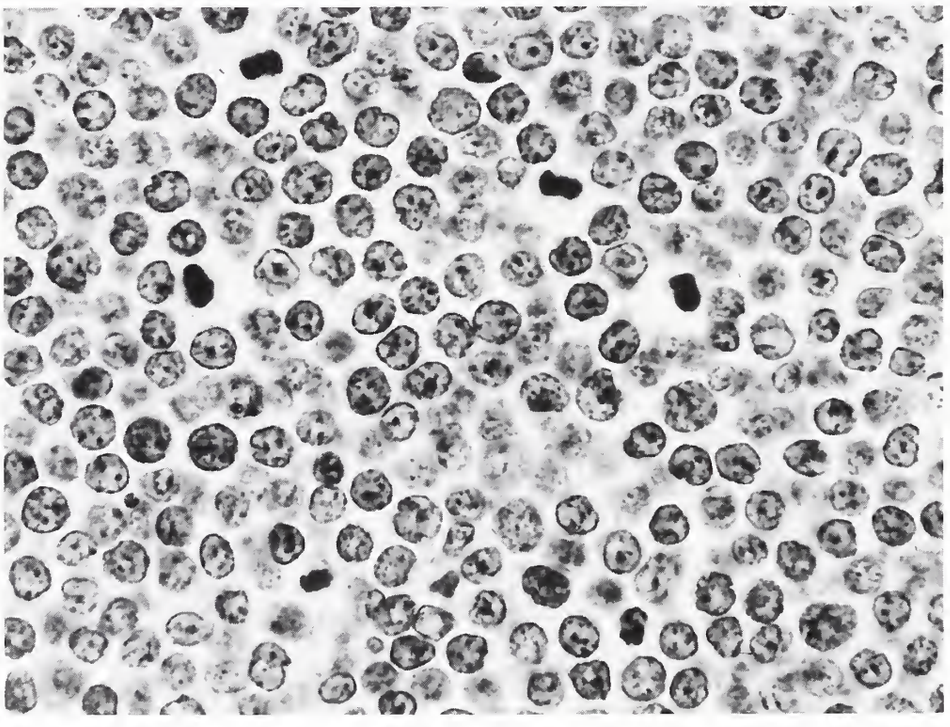


Figure 3-202
CELLULAR DETAIL OF LYMPHOBLASTIC LYMPHOMA

The neoplastic cells have an immature appearance. Scanty cytoplasm is difficult to recognize; some nuclei show clefts or infolding. (Courtesy of Dr. Koichi Shimizu, Tokyo.)

Large Cell Lymphoma

The occurrence of non-Hodgkin's, nonlymphoblastic, large cell lymphoma in the anterior mediastinum has been known for more than a decade. It is not uncommon in Europe and the United States, and many cases show a B-cell phenotype and characteristic stromal sclerosis (211,215,223,224,229,231).

Large cell lymphomas are divided into diffuse large cell lymphoma with sclerosis and large cell anaplastic lymphoma. The former is of B-cell lineage and the latter of T-cell lineage (229). However, there was no T-cell lineage case among 29 primary large cell lymphomas of the mediastinum studied by Lamarre et al. (223). In the series of Nakagawa et al. (229), diffuse large cell lymphoma with sclerosis was the most common

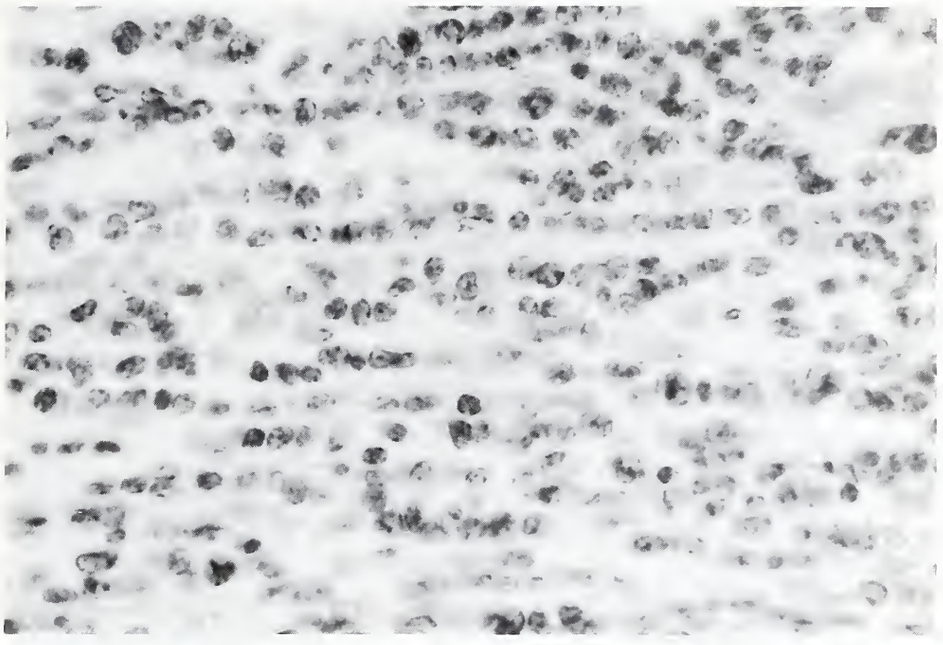


Figure 3-203
LYMPHOBLASTIC LYMPHOMA
The infiltrating neoplastic cells characteristically split the pericapsular collagen fibers and infiltrate between them in a single cell file. (Fig. 24.2 from Knowles DM. Lymphoblastic lymphoma. In: Knowles DM, ed. Neoplastic hematopathology. Baltimore, Williams & Wilkins, 1992:715–47.)

(eight cases), followed by large cell anaplastic lymphoma (five cases). We have seen 9 B-cell type diffuse large cell lymphomas, 7 with sclerosis and 2 without overt sclerosis. We have never encountered diffuse large cell anaplastic (Ki-1 positive) lymphoma, the uncommon non-Hodgkin's lymphoma, which at times involves the mediastinum and is characterized by marked nuclear pleomorphism. For details of anaplastic large cell lymphoma, see "Tumors of the Hematopoietic System," second series, Fascicle 28 and other publications (214,230).

Another group (nine cases) of rare pleomorphic large cell lymphomas of the mediastinum recently reported consisted of three different histologic growth patterns: sarcomatoid, anaplastic carcinoma-like, and lymphocyte depleted Hodgkin's disease-like patterns, causing diagnostic difficulty (236a). Immunohistochemical studies on paraffin-embedded tissue sections revealed staining of tumor cells with CD20 and CD45 antibodies, and no staining with a large panel of markers including keratin, carcinoembryonic antigen, epithelial membrane antigen, vimentin, actin, desmin, HMB45, S-100 protein, CD3, CD15, CD30, and CD45RO.

Diffuse Large Cell Lymphoma with Sclerosis. Many more cases have been reported since the original paper published by Lichtenstein et al. in 1980 (224). Miller et al. (226), in their 1981 article, referred to "diffuse histiocytic lymphoma with sclerosis," and described its characteristic histologic features and frequent mediastinal presentation, accompanied by superior vena cava syndrome. A clinicopathologic study of 60 cases was presented by Perrone et al. in 1986 (231). Since then the term mediastinal diffuse large cell lymphoma with sclerosis has been commonly used.

Prior to 1980, because of compartmentalization or nesting by hyaline connective tissue, large cell lymphomas with sclerosis were often mistaken for germinoma, undifferentiated thymic carcinoma, and Hodgkin's disease (231). In fact, the initial diagnoses of two cases seen at our center were anaplastic germinoma and undifferentiated carcinoma.

According to Perrone et al. (231), 85 percent of patients were 35 years of age or younger at the time of initial diagnosis, with a male to female ratio of about 1 to 2.5. We have seen seven cases during the past 30 years, and Nakagawa et al. (229) reported eight other cases in Japan. In these two series, the age range was 11 to 39 years (mean, 25 years) and the male to female ratio was 1 to 3.

Patients often complain of dyspnea, cough, chest pain, malaise, and fever, and not infrequently present with superior vena caval syndrome. Chest X-ray and CT examinations often disclose a large mass in the anterior mediastinum, frequently invading large vessels, pericardium, pleura, lung, and chest wall (fig. 3-204). Pleural and pericardial effusion may be present. The lesion tends to remain within the thorax, but

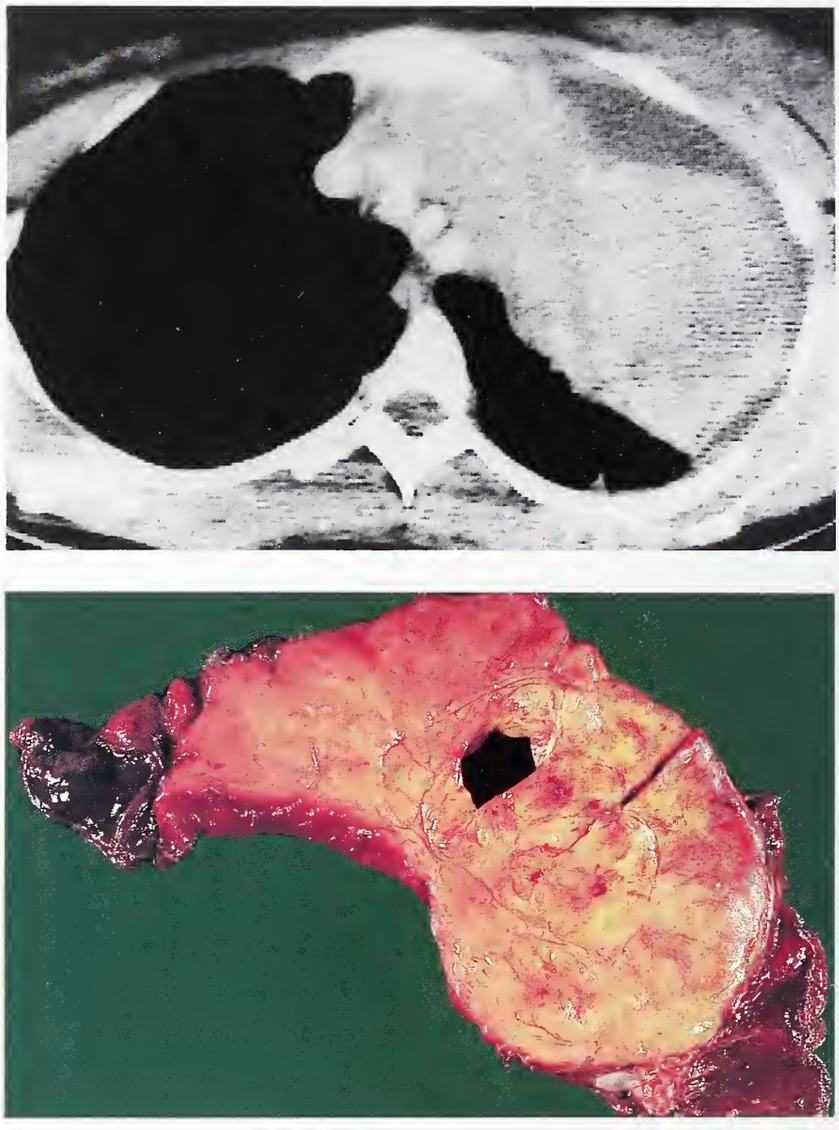


Figure 3-204
DIFFUSE LARGE CELL
LYMPHOMA WITH SCLEROSIS

Top: Enhanced CT with radiopaque material at the level above the aortic arch reveals a huge tumor which extends from the anterior mediastinum to the left thoracic cavity, replacing the left lung posteriorly. Major vessels shown from the left to right are the superior vena cava and brachiocephalic, left common carotid, and left subclavian arteries.

Bottom: Horizontal sections of the gross specimen show lobulation, conspicuous in the central portion. A small amount of the lung parenchyma (left) and a part of the chest wall (right) are attached. The hole appearing in the center is an artifact.

sometimes involves extrathoracic organs such as lymph nodes, kidney, liver, pancreas, gastrointestinal tract, central nervous system, and ovary.

Grossly, the tumor is usually larger than 10 cm in greatest dimension. The cut surface is ivory colored and there are foci of coagulation necrosis (fig. 3-205). Thymic tissue may be attached to the tumor. In smaller tumors, foci of necrosis are absent and there may be granularity due to lobulation (fig. 3-206).

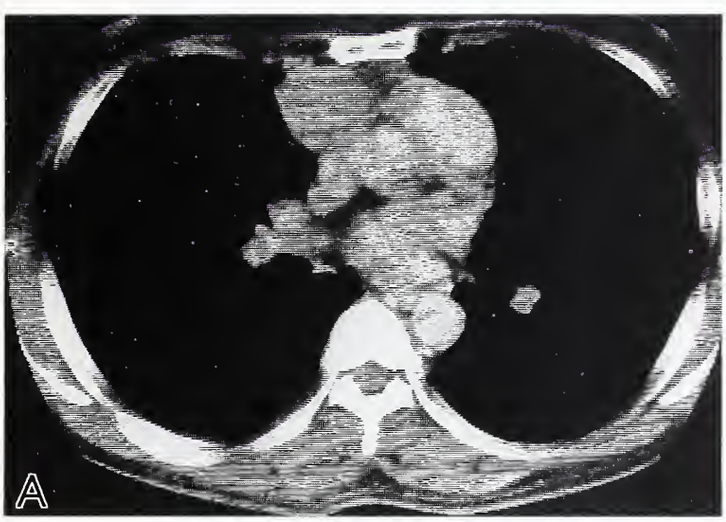
Microscopically, the tumor is often compartmentalized in various areas into epithelial tumor-like solid nests by hyaline connective tissue of varying thickness (fig. 3-207), into lobules by broad fibrous bands (fig. 3-206C), and into a spindle cell sarcomatous pattern by thin sclerotic interstitium surrounding individual tumor cells and compressing them into spindle cells.

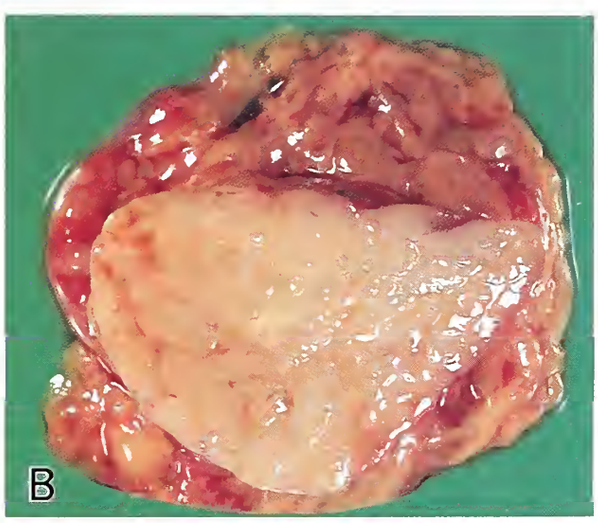
Tumor cells are large and possess abundant cytoplasm, which is pale, clear, and lightly acidophilic to basophilic. Nuclei are either large and vesicular with prominent nucleoli or indented, reniform, or even multilobated (fig. 3-208). Fixation artifacts, such as dense nuclei and apparently empty or vacuolated cytoplasm, may be seen. Mitotic figures are frequently observed. In one study, Azur granules were seen in the cytoplasm in imprint smears stained with May-Giemsa stain; these are said to be rare in nodal B-cell tumors (229).

Immunohistochemically, tumor cell phenotypes are CD5-, CD10-, CD19+, CD20+, CD21-, and CD22+ (fig. 3-209) (229). SIg and CIg are often negative, and when positive, are of IgG or IgA type, contrasting with the IgM or IgD types seen in large cell lymphoma of nodal origin

Figure 3-205
DIFFUSE LARGE CELL LYMPHOMA WITH SCLEROSIS

The horizontal cut surface of the large tumor shows invasive growth into the left upper lobe of the lung and irregular areas of coagulation necrosis. Lobulation is inconspicuous due to the high cellularity.





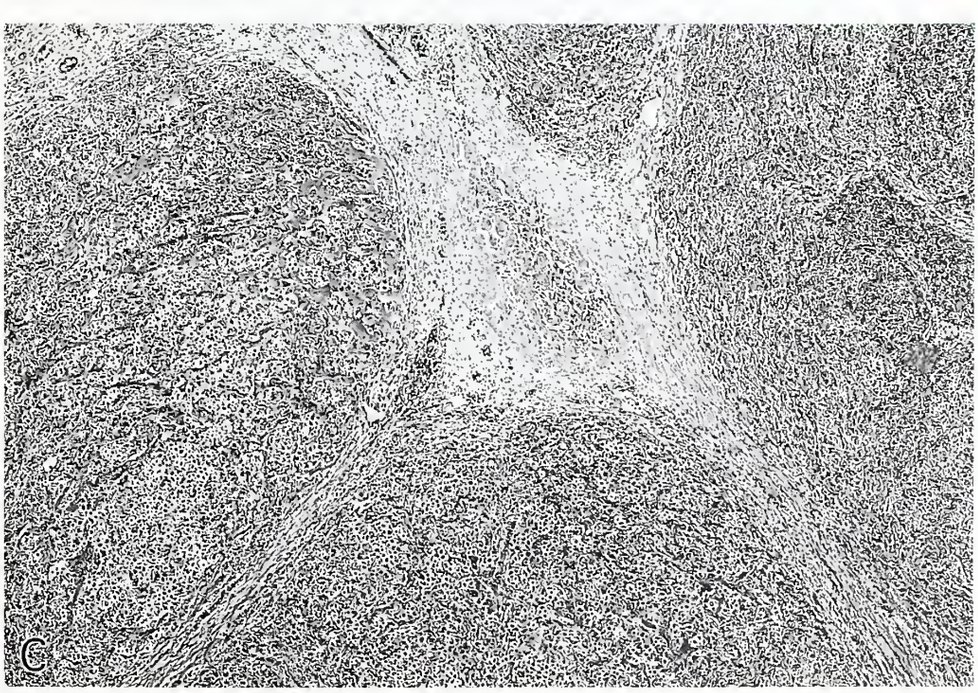


Figure 3-206
DIFFUSE LARGE CELL LYMPHOMA WITH SCLEROSIS

A: Enhanced CT at the level below the tracheal carina discloses a rather homogeneous tumorous density with smooth borders anterior to the heart, and adjacent to the pericardium and right lung.

B: Horizontal cut surface of the tumor shows lobulation and nodularity without foci of coagulation necrosis.

C: Low-power micrograph of the tumor shows lobulation with fibrous bands resembling nodular sclerosis type Hodgkin's disease.

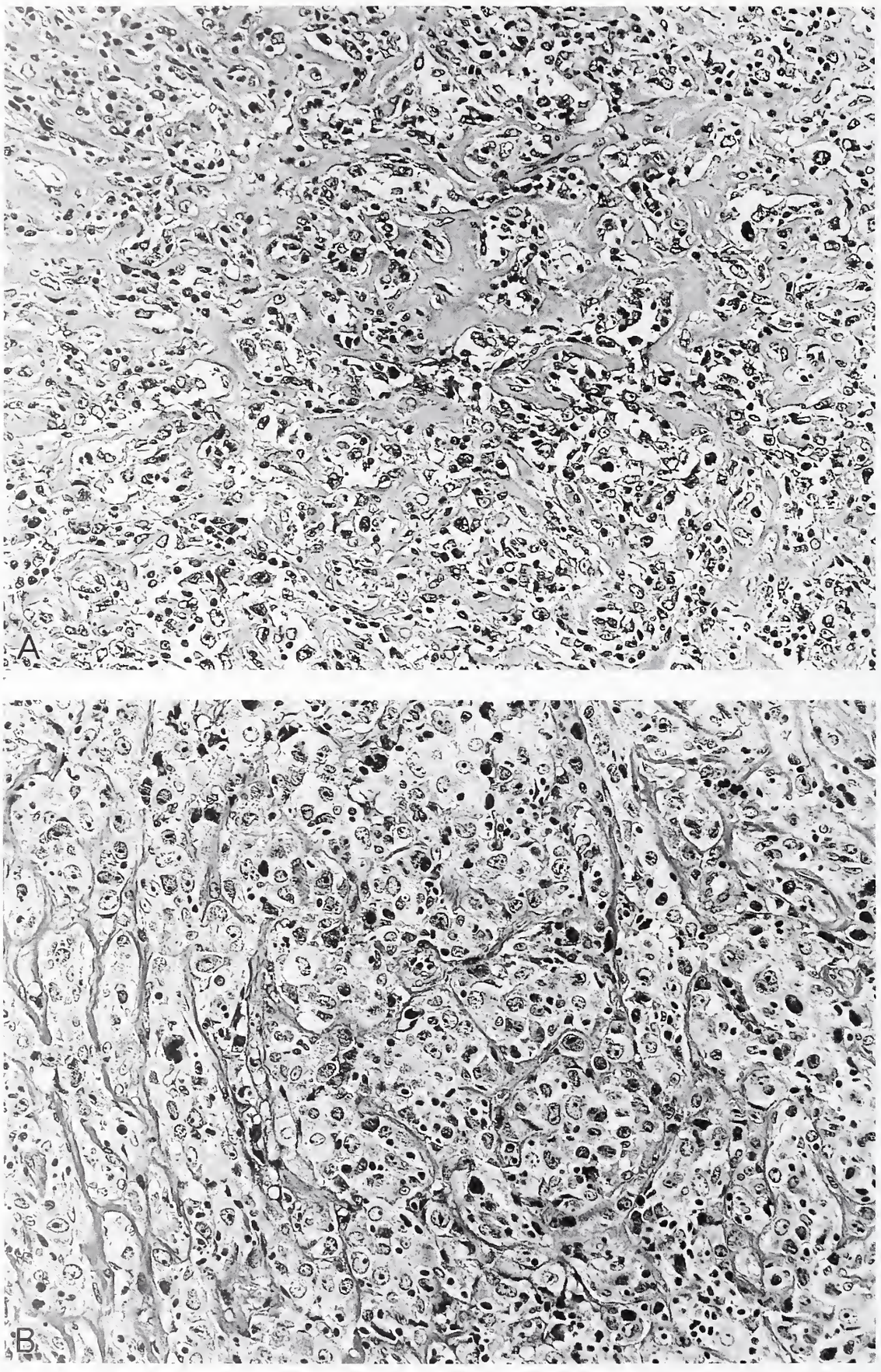


Figure 3-207
DIFFUSE LARGE CELL LYMPHOMA WITH SCLEROSIS
Compartmentalization by interstitial sclerosis of various degrees is shown in A–C.

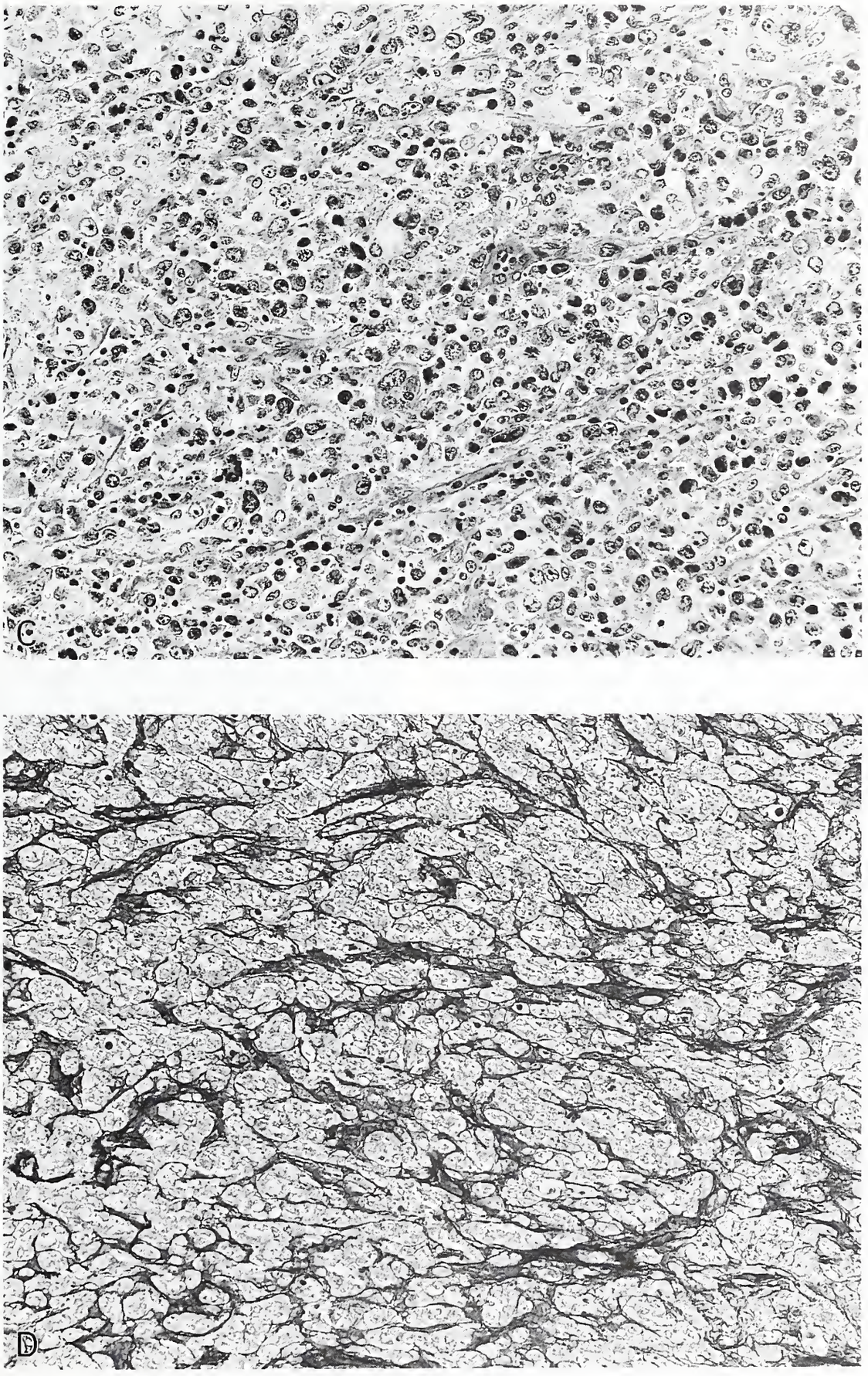


Figure 3-207 (Continued)
Silver impregnation (D) shows both complete and incomplete compartmentalization.

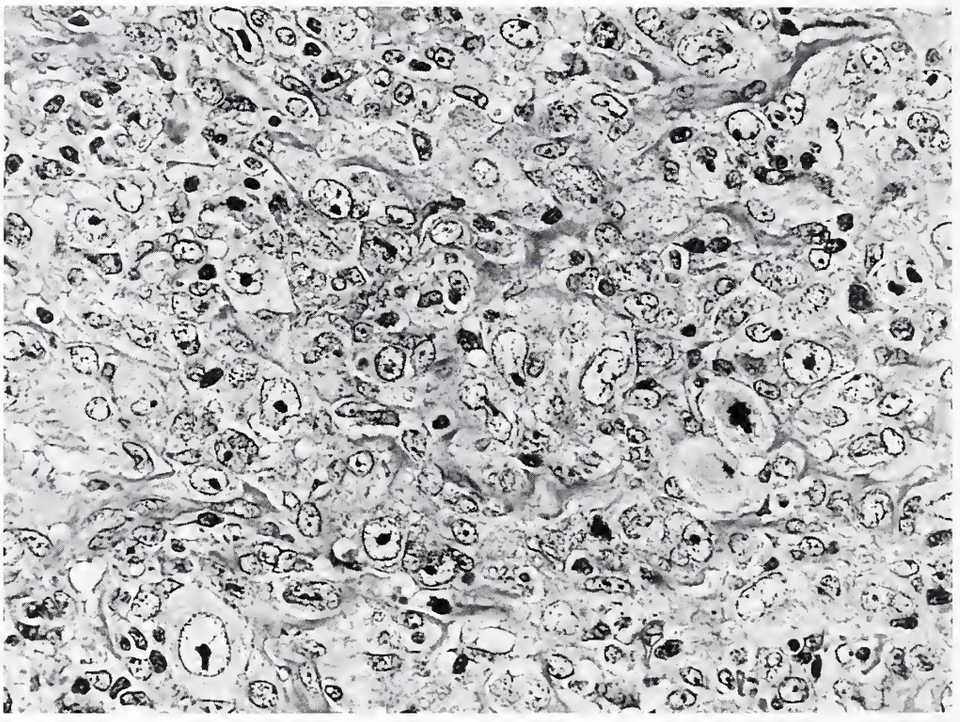


Figure 3-208
DIFFUSE LARGE CELL LYMPHOMA WITH SCLEROSIS

Higher magnification discloses large tumor cells with abundant pale cytoplasm, round to reniform vesicular nuclei, and prominent nucleoli. A mitotic figure is noted. Most small lymphoid cells are of reactive T-cell phenotype.

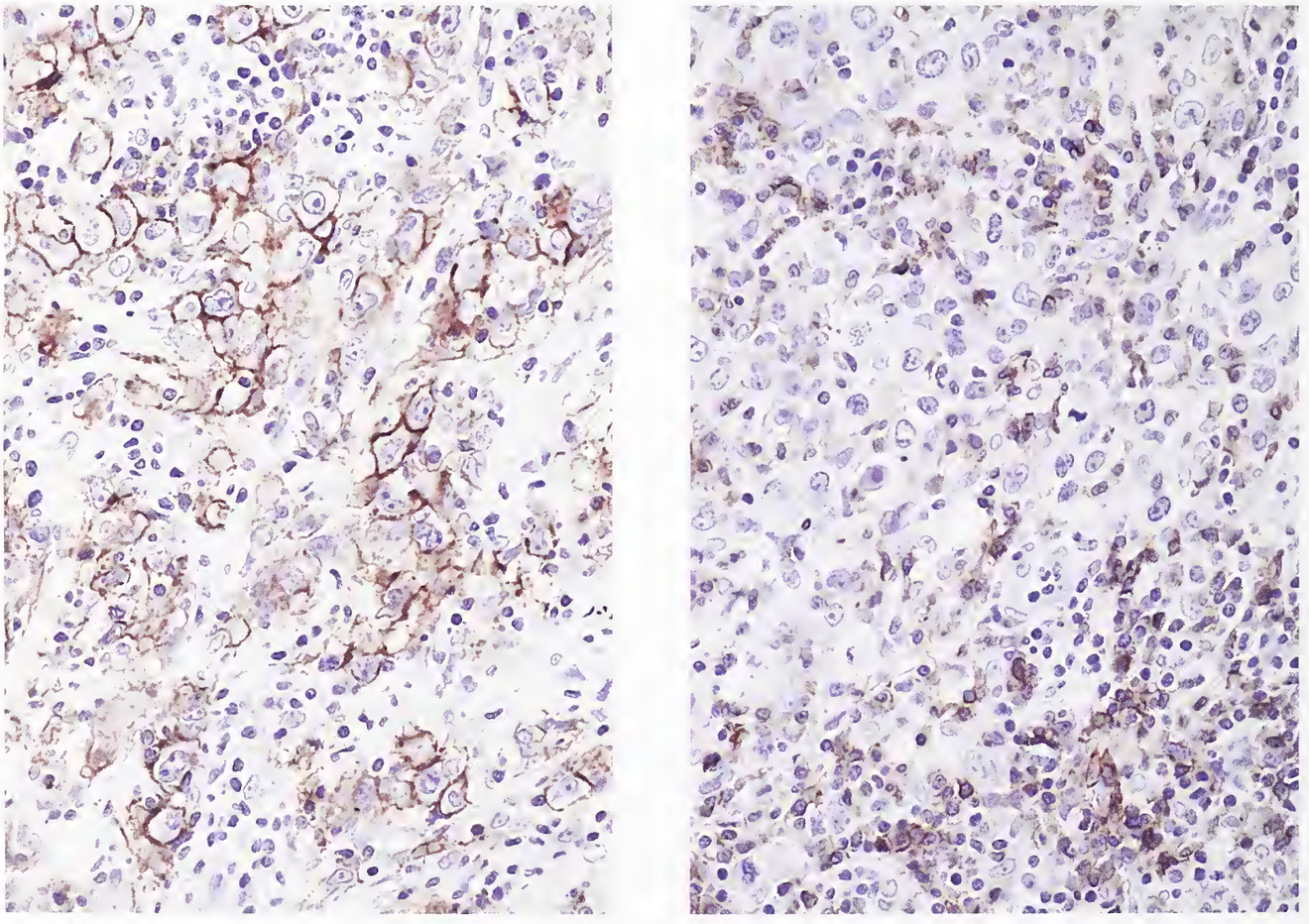


Figure 3-209
DIFFUSE LARGE CELL LYMPHOMA WITH SCLEROSIS

Immunohistochemically, tumor cells show marked membrane staining with CD20 (L26) antibody (left), and no reactivity with CD45RO (UCHL-1) antibody (right), indicating a B-cell phenotype. Small lymphocytes of a reactive nature are strongly positive for UCHL-1 (T cell).

(223,236). Negative CD21 suggests an origin from B cells present in the normal thymus (218).

Southern blot analysis has disclosed unique heavy and kappa-light chain immunoglobulin gene rearrangements, thereby genotypically establishing a B-cell origin and a germ-line T-cell receptor gene in all but one case (229,234). C-*myc* gene alterations were found in three of six cases, none of which displayed a *bcl*-2 gene rearrangement or contained Epstein-Barr viral sequences (229,235). Analysis of molecular genetic pattern in 16 cases of primary mediastinal large B-cell lymphoma revealed infrequent occurrence (6 percent) of *bcl*-6 gene rearrangement as compared with other diffuse large B-cell lymphomas (up to 45 percent), suggesting that primary mediastinal large B-cell lymphomas do represent a distinct subtype of diffuse large B-cell lymphoma (237a).

Initially, the prognosis of patients with large cell lymphoma with sclerosis was reported to be poor. Unfavorable prognostic factors were age less than 25 years at diagnosis, tumor outside the thoracic cavity, disease recurrence, and immunoblastic tumor histology. Favorable signs were good response to initial therapy and marked tumor sclerosis (231). Recently, prognosis has improved and a 5-year survival rate of about 50 percent is obtained with intense chemotherapy combined with radiotherapy (220,223,229).

Differential diagnoses include germinoma, undifferentiated thymic carcinoma, Hodgkin's disease, mediastinal involvement of diffuse large cell and immunoblastic lymphoma of extrathoracic origin, metastatic undifferentiated carcinoma of extrathoracic origin, and metastatic amelanotic melanoma.

Clear Cell Lymphoma of B-Cell Type. Another rare primary B-cell lymphoma in the mediastinum was reported by Möller et al. (227) in young adults aged 19 to 43 years (mean, 29.4 years) and predominating in females (8 to 6). Histologically, it is characterized by a diffuse growth of pleomorphic tumor cells that have abundant clear cytoplasm and vary in size and nuclear morphology according to each individual. Tumor cells show a moderately to extremely high S-phase component and rapid growth. Most patients respond poorly to aggressive chemotherapy: in Möller's study, five out of eight patients died 10 to 22 months after diagnosis. Immunophenotypes were leukocyte common antigen (LCA)+, CD19+, CD20+, CD21-, CALLA-, and immunoglobulin (Ig)-, corresponding to the terminal steps of B-cell differentiation (227,228). Subsequently, clonal immunoglobulin gene rearrangements were demonstrated in two cases of mediastinal clear cell lymphoma (212).

Atypical Hyperplastic Lymphoepithelial Lesion and Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

In 1987, Isaacson and Spencer (219) reviewed malignant lymphomas of mucosa-associated lymphoid tissue (MALT) that involved the gastrointestinal tract, salivary gland, lung, and thyroid; most were of B-cell type and tended to remain localized for prolonged periods. In 1990, Isaacson et al. (217) reported two cases of low-grade B-cell lymphoma of MALT arising in the thymus; this was followed by a report of a similar case but with associated Sjögren's syndrome by Takagi et al. (237). The cases were characterized by "lymphoepithelial lesions," most closely resembling MALT lymphoma arising in myoepithelial sialadenitis, and in the thymus Hassall corpuscles were considered to correspond to a mucosal structure.

The reported tumors were encapsulated masses of 9 to 12 cm in greatest dimension, with a pale tan homogeneous cut surface studded with fluid-filled cysts of up to a few centimeters in diameter. Histologically, the normal architecture of the thymus was obscured by lymphoid infiltrate, in which Hassall corpuscles survived. The lymphoid infiltrate consisted of reactive type follicles and diffuse growth of predominantly "centrocyte-like lymphocytes," which possessed variably irregular nuclei; abundant clear, faintly granular cytoplasm; and sharp cell borders. Larger blast forms and plasma cells were also scattered. Mitotic counts were reported to be less than 1 per 10 high-power fields. Cysts were lined by attenuated epithelium infiltrated by centrocyte-like lymphocytes and contained eosinophilic proteinaceous fluid. Lymphoid infiltrates consisted largely of B cells, which were revealed by L26 reactivity. Both of the cases of Isaacson et al. showed kappa light chain restriction, expressing IgM in case 1 and IgA in case 2. In the case of Takagi et al., the cells were monotypically stained with IgA and kappa light chain. The phenotypes of centrocyte-like lymphocytes were CD22+, IgD-, CD5-, CD10-, and KB61+. The

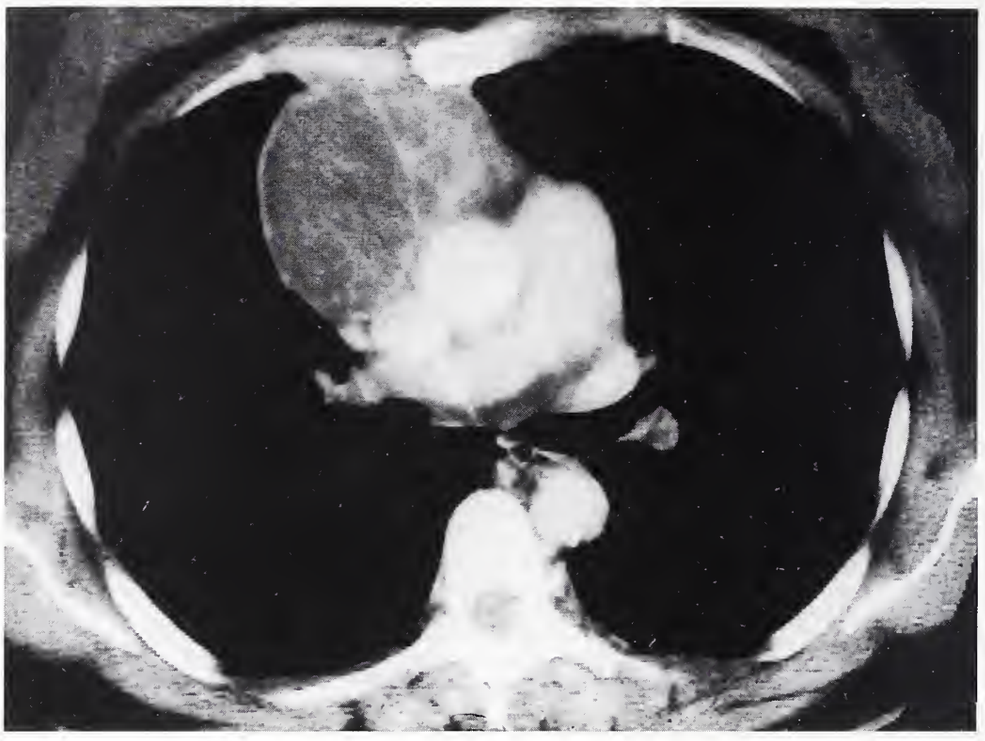


Figure 3-210
PROBABLE LOW-GRADE B-CELL LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) OF THE THYMUS

CT at the level of the right pulmonary artery enhanced with radiopaque material reveals a roughly oval, clearly defined tumor with a smooth border in the anterior mediastinum, which is lobulated and nonhomogeneous, strongly suggestive of a multiloculated cystic lesion. Preoperative diagnosis was cystic teratoma. (Figures 3-210–3-213 are from the same case.)

tumor reported by Takagi et al. revealed rearrangements of the immunoglobulin heavy chain-joining region gene, kappa light chain-joining region gene, and the T-cell receptor beta-chain gene constant region.

Low-grade B-cell lymphomas of MALT are often localized when diagnosed, are relatively benign, and may be cured by surgical resection. In case 1 of Isaacson et al. (217) the patient was alive and free of disease 4 years after surgery without further treatment; in case 2, tumor involved a left axillary lymph node which was excised 2 months after resection of the thymic lymphoma. The patient reported by Takagi et al. (237) underwent total surgical resection of the mediastinal tumor, which was 13 cm in the greatest dimension and confined to within the thymus except at a small area that involved the pericardium. An adjacent lymph node was also involved. Resection was followed by radiotherapy and the patient was in complete remission 20 months later.

We saw two cases very similar to low-grade B-cell lymphoma of MALT. In the first case, an unusual asymptomatic anterior mediastinal tumor was detected by routine chest X-ray examination in a 43-year-old Japanese housewife. It was multicystic on CT scan (fig. 3-210) and preoperatively suspected to be a teratoma. The resected thymic tumor was 10 x 8.5 x 2 cm and weighed 125 g. The cut surface of the mass revealed a thinly encapsulated tumor with multiple, irregular cystic spaces varying in size, and intervening pale tan medullary tissue (fig. 3-211, top).

Histologically, seen attached to the tumor was scanty thymic tissue of normal appearance for the patient's age. The tumor itself was lobulated, with cystic spaces within lobules and a few fat cells between lobules (fig. 3-211, bottom). Cortices and medullae were indistinct but enlarged Hassall corpuscles could be recognized. Cystic spaces containing serous fluid, lymphoid cells, and degenerated Hassall corpuscles, with or without calcification, were bordered by atypical hyperplastic thymic tissue with squamoid epithelium infiltrated by lymphocytes. The lesion was considered to be lymphoepithelial (fig. 3-212). Some cystic spaces were devoid of lining epithelium and bordered lymphoid tissue directly. No perivascular spaces or other structures characteristic of thymoma were seen. Lymph follicles with germinal centers were seen in some areas (fig. 3-212, bottom). There was diffuse growth of uniform, medium-sized lymphoid cells that had round granular nuclei, small nucleoli, and clear, faintly granular cytoplasm. Cell borders were not very distinct (fig. 3-213, left). Mitotic figures were rare. There were scattered larger blast-like cells.

Figure 3-211

PROBABLE LOW-GRADE B-CELL LYMPHOMA OF MALT OF THE THYMUS

Top: The cut surface of the tumor shows variously sized, multiple cystic spaces with intervening medullary pale tan tissue.

Bottom: Low-power magnification reveals a partly thinly encapsulated tumor, which is lobulated. A few fat cells are between the lobules. Irregular cystic spaces containing serous fluid are present within or in association with lobules. At the top of the photograph, scanty thymic tissue is attached to the tumor.

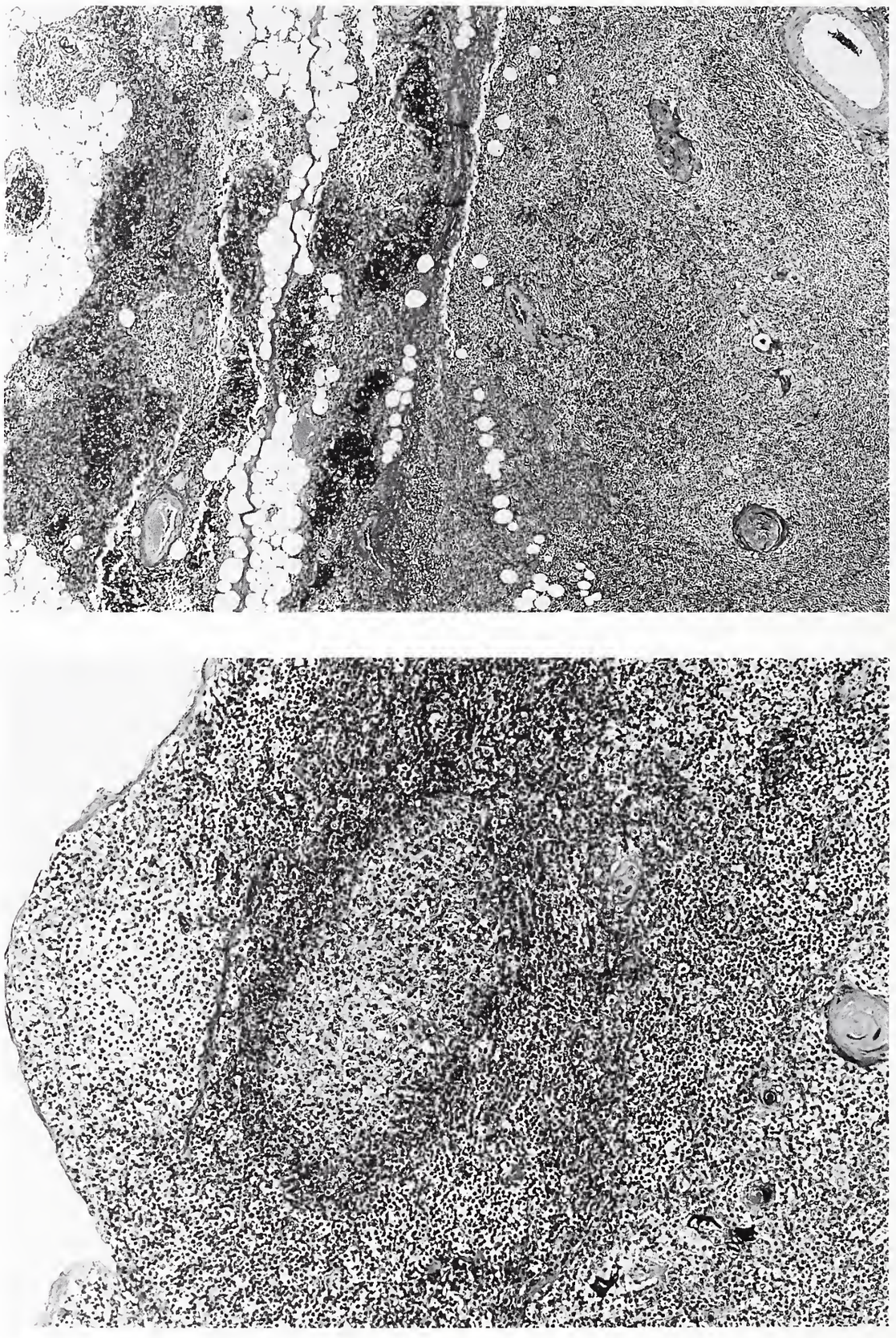


Figure 3-212
PROBABLE LOW-GRADE B-CELL LYMPHOMA OF MALT OF THE THYMUS

Top: Thymic tissue of normal appearance is shown on the left. The tumor, which is on the right, contains prominent Hassall corpuscles. Medullae and cortices are still recognizable, although somewhat blurred in some areas.

Bottom: A cyst is lined by attenuated squamoid epithelial cells, beneath which is a small monotonous area consisting of uniform clear lymphoid cells facing a lymph follicle with a germinal center. On the right, a Hassall corpuscle is surrounded by atypical clear lymphoid cells.

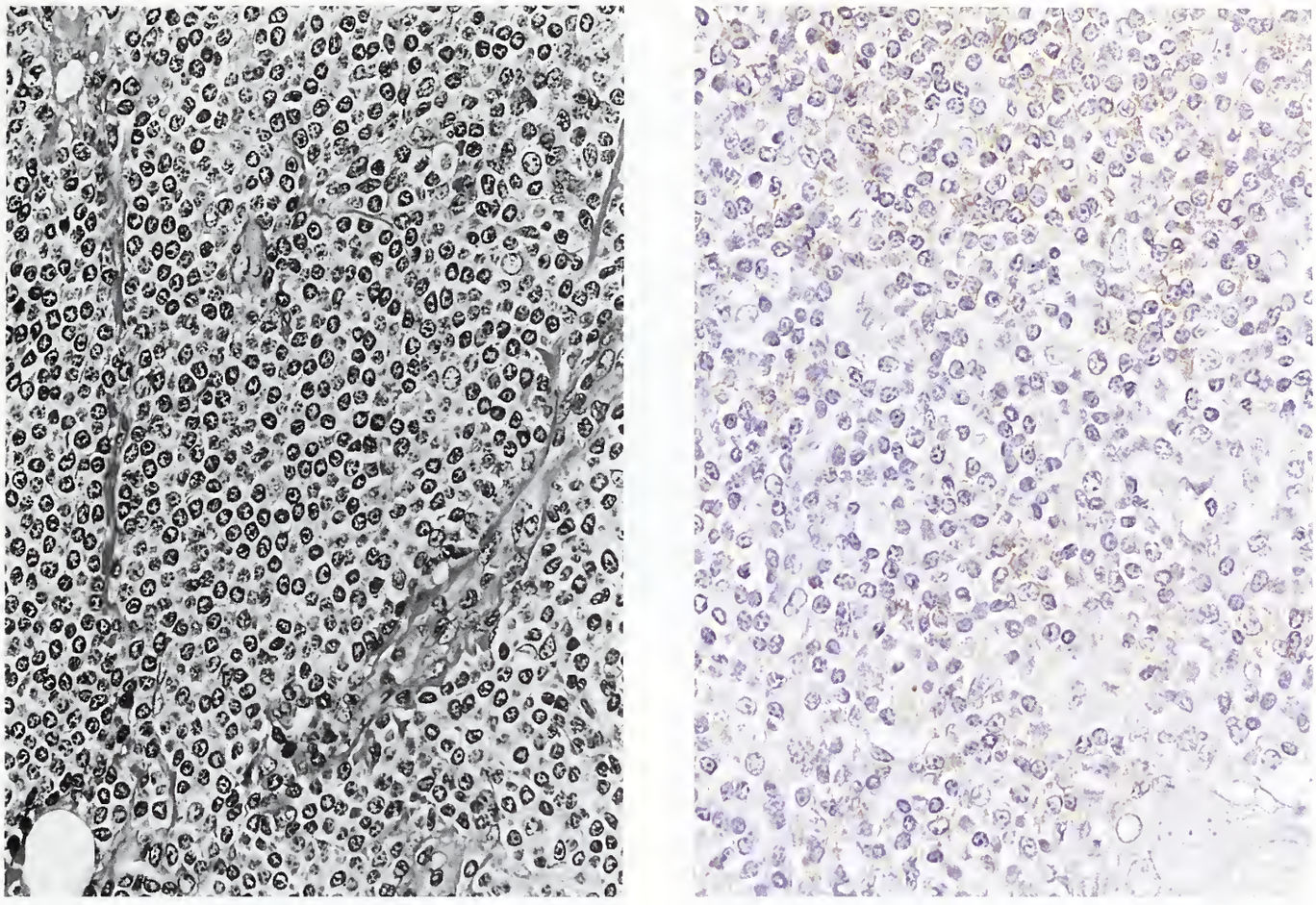


Figure 3-213
PROBABLE LOW-GRADE B-CELL LYMPHOMA OF MALT IN THE THYMUS
Left: High magnification of the tumor reveals diffuse monotonous growth of medium-sized lymphoid cells with round granular nuclei, small nucleoli, and clear granular cytoplasm. The cell border is indistinct in this case. Mitotic figures are not seen.
Right: L26 immunostaining reveals many positive cells and scattered large blast-like cells. A Hassall corpuscle is seen at the right lower corner.

This atypical lymphoid tissue infiltrated the thymic cortices and medullae and formed parts of the cyst walls.

Originally, because of lack of awareness of such a lesion in the thymus; clear delineation of the lesion from normal thymic tissue; the presence of thymic tissue components such as Hassall corpuscles, lymphoid cells, and fat; and no definite features suggestive of malignancy, we diagnosed the lesion as a hamartoma of the thymus, although no such entity had ever been reported. However, because atypical lymphoid cells were revealed with L26 reactivity (fig. 3-213), we now consider that this lesion is most likely a low-grade B-cell lymphoma of MALT primary in the thymus, although restriction of light chain expression could not be verified and the possibility of a hyperplastic lymphoepithelial lesion with atypia cannot be ruled out. The patient is alive with no evidence of recurrence 9 1/2 years after surgery.

The second case was a 51-year-old female who complained of back pain and was found to have an anterior mediastinal tumor by CT examination. The tumor was solid, 7.5 x 6.2 x 2.0 cm in size, weighed 50 g, was confined to within the thymus, and was in continuity with the thymic parenchyma. Scattered within the tumor were lymph follicles with germinal centers. Medullae of the thymus were almost completely replaced by monotonous, medium-sized monocytoid cells, characterized by moderately abundant, clear or very finely granular cytoplasm and round or indented

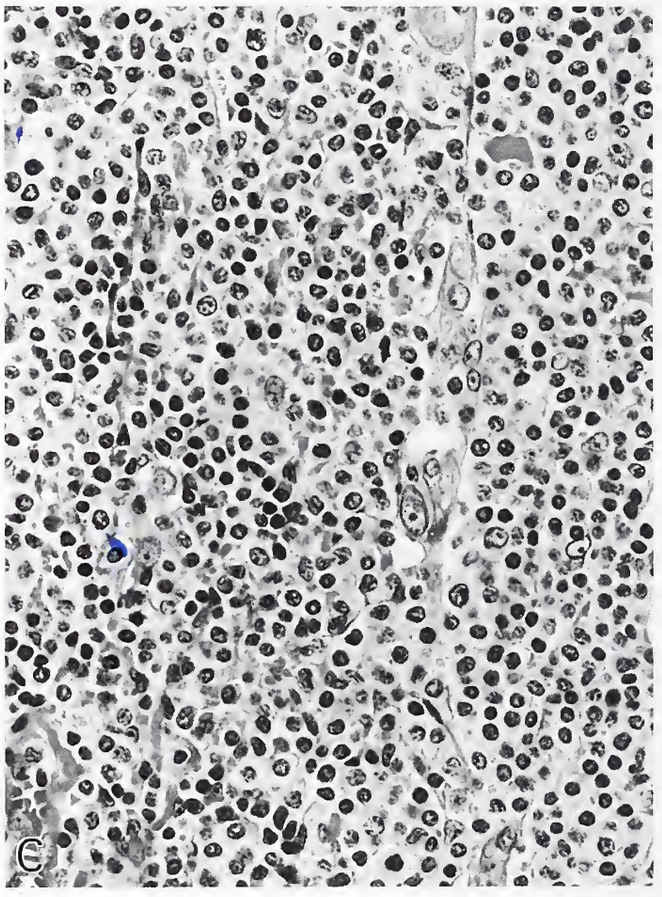


Figure 3-214
LOW-GRADE B-CELL LYMPHOMA OF MALT IN THE THYMUS

A: Low-power photograph reveals a nonencapsulated, in part lobulated, nodular tumor abutting on the involuting thymus. The tumor is studded with multiple pale zones, but no cystic changes are seen. (Figures 3-214 and 3-215 are from the same case.)

B: Histologically, medullae of the thymus have been almost completely replaced by monotonous growth of small round cells surrounding a well-formed Hassall corpuscle, adjacent to which is a lymph follicle with a germinal center.

C: Higher power magnification reveals that the proliferating cells surrounding attenuated Hassall corpuscles are medium-sized monocytoid cells with clear cytoplasm and round or indented nuclei. A few mitotic figures are seen.

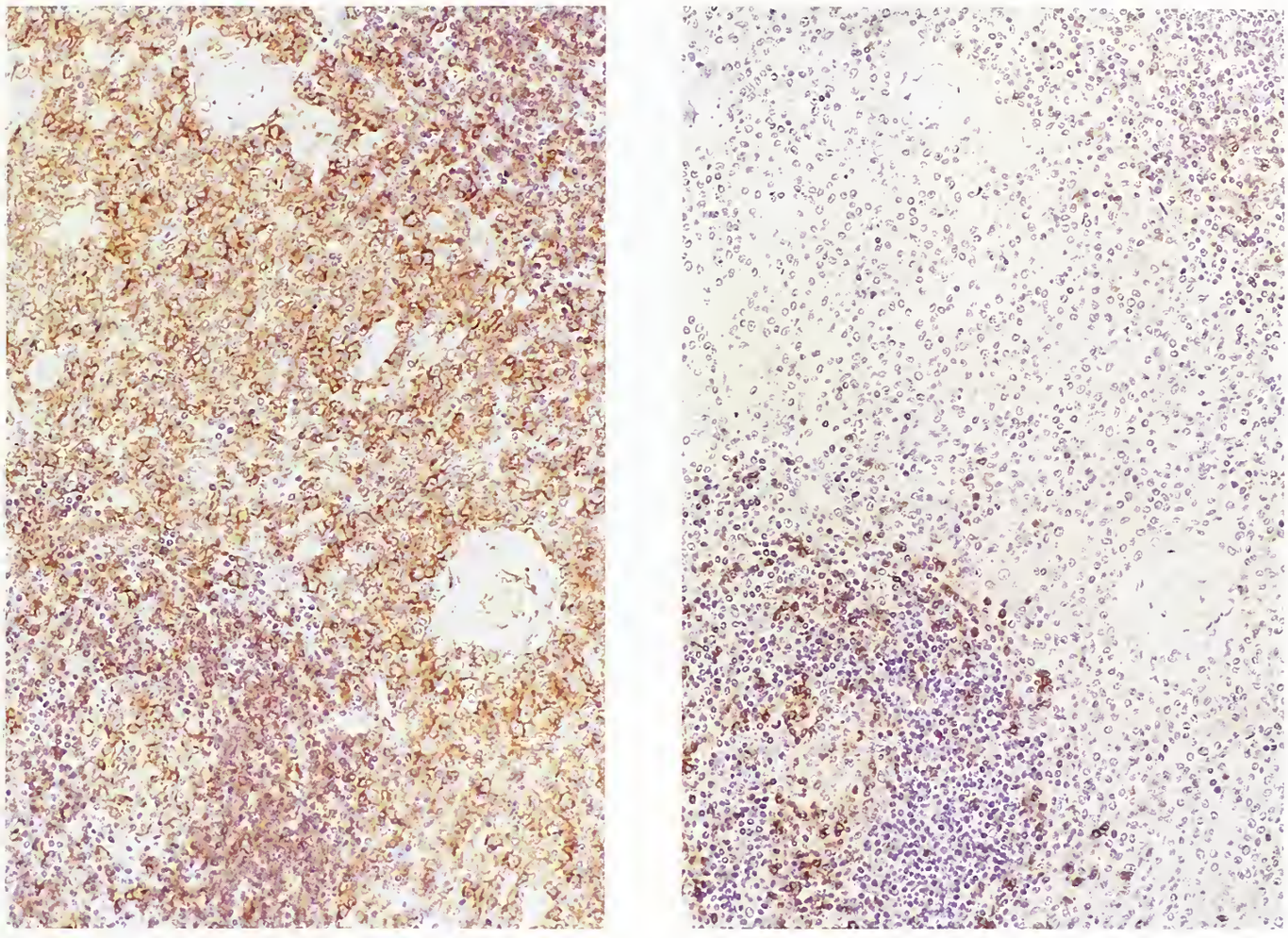


Figure 3-215
LOW-GRADE B-CELL LYMPHOMA OF MALT IN THE THYMUS
Left: A Hassall corpuscle is surrounded by diffuse growth of atypical monocytoid B lymphocytes reactive with L26 antibody. Right: Almost no T lymphocytes reactive with UCHL-1 antibody remain in a zone with diffuse growth of atypical B lymphocytes. (Immunostain of serial sections with L26 [left] and UCHL-1 [right])

nuclei. Mitotic figures were occasionally seen (fig. 3-214). However, follicular colonization was not evident on hematoxylin and eosin-stained sections. Immunohistochemically, atypical monocytoid cells were found to be of B-cell phenotype, showed kappa light chain restriction, and expressed IgA (fig. 3-215). The diagnosis was localized MALT lymphoma.

Low-grade B-cell lymphomas of MALT appear to have an indolent clinical course. The relationships among atypical hyperplastic MALT, low-grade B-cell lymphoma of MALT, and high-grade mediastinal B-cell lymphomas such as large cell lymphoma with sclerosis remain to be investigated.

SECONDARY INVOLVEMENT OF THE THYMUS BY CARCINOMA AND MESOTHELIOMA (INCLUDING SOLITARY FIBROUS TUMOR)

Secondary Carcinoma Involving the Thymus

The mediastinum, particularly the anterior mediastinum, is frequently involved by carcinoma of various organs, either by direct extension from neighboring organs or via mediastinal lymph node metastasis; hematogenous metastasis to the thymus is rare.

Carcinoma of the lung involves the thymus more frequently than carcinoma of other organs

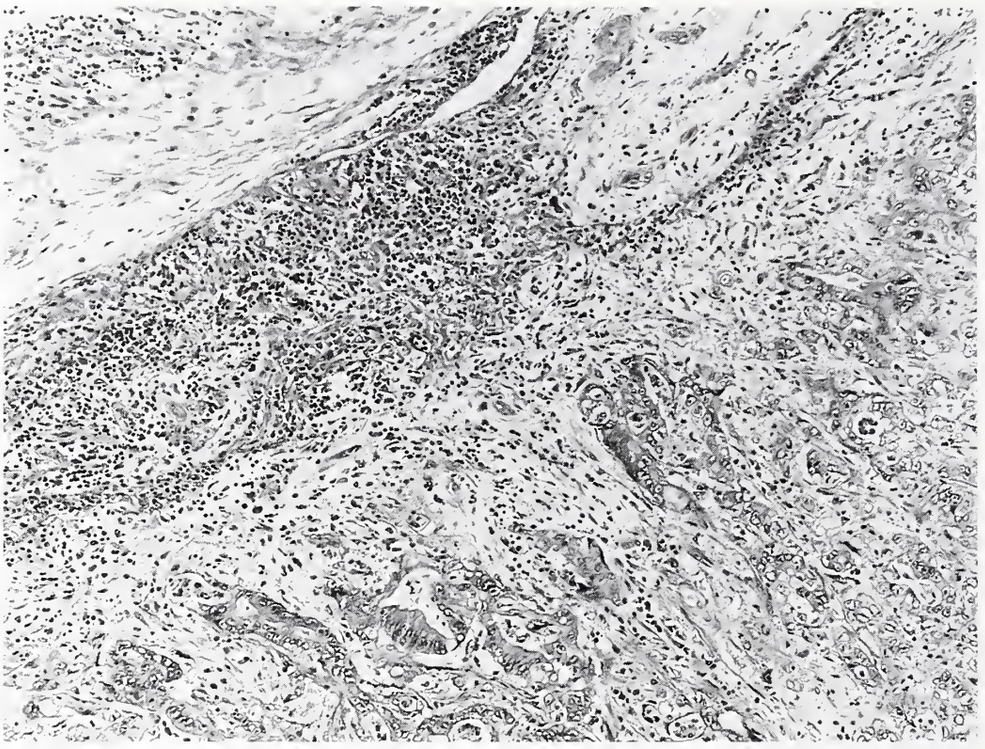


Figure 3-216
METASTATIC CARCINOMA IN THE THYMUS
Nests of moderately differentiated adenocarcinoma, the primary of which was in the lung, invade a lobule of atrophic thymus.

(fig. 3-216), usually by direct invasion of both hilar and peripheral types. All of the major histologic types of lung cancer can involve the thymus. Other routes of cancer spread include downward growth of thyroid cancer and cancers of the head and neck region, anterolateral extension of tracheal carcinoma, and extension through the chest wall by breast carcinoma. Involvement of the thymus through lymph node metastasis to the anterosuperior mediastinum occurs in cancer of various organs, not only from the lung and breast but also from abdominal organs, pelvis, and head and neck region such as stomach, prostate, and tongue.

Unless the primary is clinically latent, the source of metastasis to the thymus is easily recognized because of the generally advanced stage of the primary tumor. Even when the primary is clinically latent, the histology of the tumor suggests the primary site in many cases.

Distinction Between Thymic and Pulmonary Carcinomas

As described in the chapter on thymic carcinoma, there are many identical and similarly named tumors in the thymus and lung: squamous cell carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, undifferentiated large cell carcinoma, small cell/neuroendocrine carcinoma, sarcomatoid carcinoma, and carcinoid tumors. If the tumor is confined to within one organ, diagnosis can be made with ease. If the tumor involves both organs in continuity, the primary site may be difficult to determine.

The section on thymic carcinoma details the characteristic features of well-differentiated thymic squamous cell carcinoma that distinguish it from bronchial squamous cell carcinoma, such as nuclear features and broad sclerotic stroma (see figs. 3-109–3-111). No distinctive histologic differences are present in poorly differentiated squamous cell carcinoma, small cell carcinoma, and carcinoid tumors. In those cases, the gross topographic relationship of the tumor with the two organs and the location of the area with the most abundant stroma or coagulation necrosis, which suggests the site of origin of the tumor, helps identify the primary site of the tumor. Small cell carcinoma of the lung frequently forms a large mass in the anterior and middle mediastinum, and this had even been designated mediastinal sarcoma until 1926 (238).

While extremely rare, carcinoma originating in the epithelial inclusion in a lymph node or extrathymic mediastinal soft tissue is possible (243). We saw a case of small cell (typical oat cell) carcinoma in the middle mediastinum involving a lymph node of the left pulmonary hilus in a

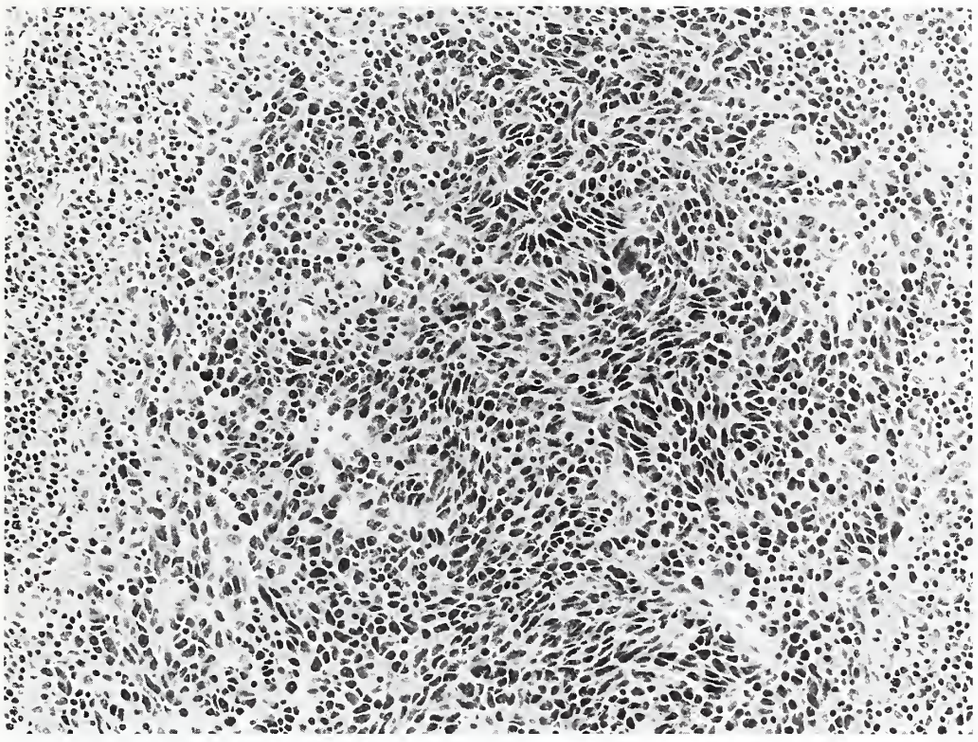


Figure 3-217
SMALL (OAT) CELL CARCINOMA IN A PULMONARY HILAR LYMPH NODE
Small tumor cells, typical of oat cell type, grow within a lymph node of the left pulmonary hilus.

65-year-old male, in which no primary tumor was found in the resected but otherwise unremarkable left upper lobe of the lung. The patient survived for more than 10 years without recurrence (fig. 3-217). This could well be a case of spontaneous regression of the primary lung cancer but the possibility of small cell carcinoma originating in a lymph node cannot be overlooked.

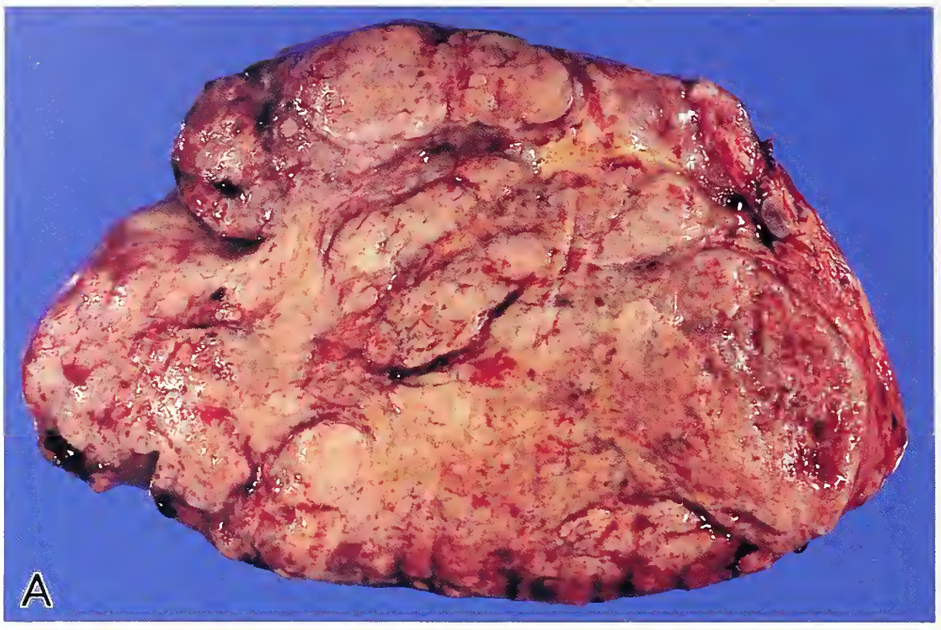
Mesothelioma Involving the Thymus and Solitary Fibrous Tumor

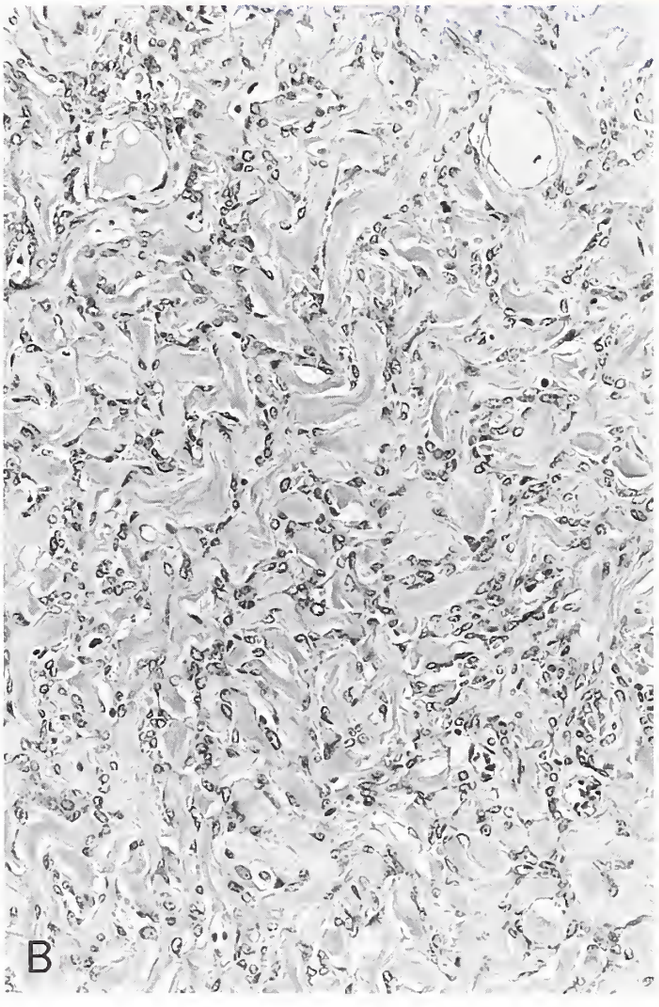
Malignant pleural mesothelioma of the diffuse type may invade the thymus in continuity, but involvement is almost always superficial. Mixed polygonal and spindle cell thymoma and sarcomatoid carcinoma of the thymus may mimic biphasic fibrous and epithelial mesothelioma. However, the mode of local growth, extension, and spread, together with some difference in cytologic appearance, can assist in the differential diagnosis.

So-called benign localized mesothelioma of the fibrous type (localized fibrous tumor of the pleura) may show nodular growth within the thymus or mediastinum, with or without connection to the pleura or pericardium (fig. 3-218A). It possesses characteristic features and can be distinguished from spindle cell thymoma histologically and immunohistochemically. Fibroblast-like tumor cells are often aligned like strings of beads in a somewhat myxoid matrix or between collagen bundles, or arranged in bundles in cellular areas (fig. 3-218B,C).

Immunohistochemically, tumor cells are negative for cytokeratin, muscle actin, and glial fibrillary acidic protein, and positive for vimentin and CD34 (fig. 3-219) (242,244,245). In one study, tumor cells in some cases were focally positive for desmin and negative for CD34 (244). CD34 antigen, originally described as a marker for human hematopoietic stem cells, is expressed in a diverse group of neoplasms including leukemia, vascular tumor, hemangiopericytoma, nerve sheath tumor, epithelioid sarcoma, smooth muscle tumor, and solitary fibrous tumor. Reaction with CD34 antibodies can be diagnostically helpful since CD34 antigen tends to be absent from many common tumors such as carcinoma, melanoma, lymphoma, and most types of sarcoma (245). Histologically, malignant solitary fibrous tumor with hypercellularity, some proliferative activity, and foci of coagulation necrosis is rare (fig. 3-220), and always poses a diagnostic problem; immunohistochemistry may be of help diagnostically (242,244,245).

Of 14 patients with solitary fibrous tumor of the mediastinum reported by Witkin and Rosai (246), two had accompanying hypoglycemia. Eleven tumors were in the anterosuperior mediastinum,





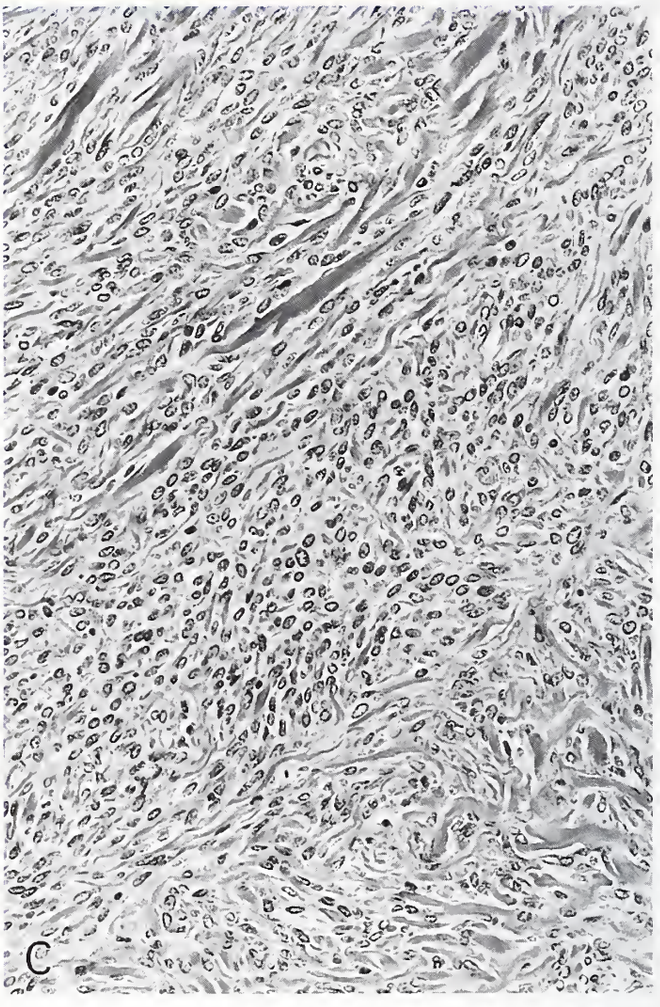


Figure 3-218
LOCALIZED BENIGN FIBROUS TUMOR OF THE PLEURA

A: Grossly, a largely encapsulated huge tumor shows a bulging, partly nodular and partly lobulated cut surface, with small foci of lytic degenerative change. (Figures 3-218 and 3-219 are from the same case.)

B: Fibroblast-like tumor cells with oval nuclei are aligned like strings of beads or have a rosary-like configuration around collagen fibers.

C: In highly cellular areas, tumor cells are arranged in bundles or haphazardly with scanty collagen.

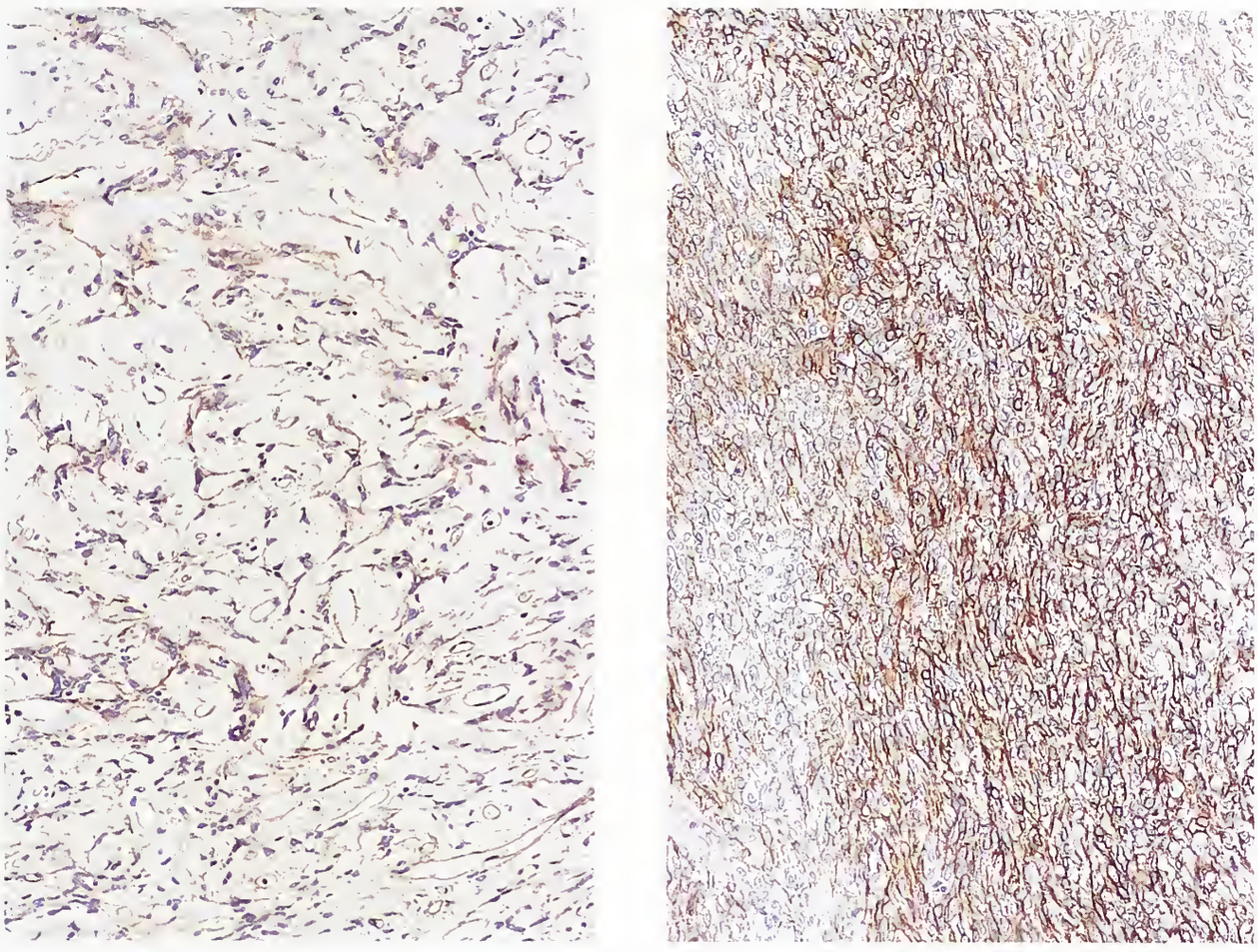


Figure 3-219
LOCALIZED BENIGN FIBROUS TUMOR OF THE PLEURA
Immunohistochemically, tumor cells stain for CD34 in both less cellular (left) and highly cellular (right) areas.

one arose on a pedicle from the thymus, and another had entrapped thymic elements. Eight tumors were highly cellular and mitotically active, many behaving aggressively with occasional recurrence and rare distant metastasis. The differential diagnosis includes spindle cell thymoma and peripheral nerve tumors.

Recent immunohistochemical and ultrastructural studies on localized benign and malignant fibrous tumors of the pleura indicate that these tumors are probably derived from submesothelial connective tissue cells rather than from mesothelial cells, and the term "localized fibrous tumor" of the pleura is recommended instead of "localized fibrous mesothelioma" (241,246). Carter and Otis (239) described three types of fibrous tumors of the pleura: 1) a localized, histologically benign, keratin-negative spindle cell tumor that might be termed fibroma; 2) a diffuse, histologically malignant, keratin-positive tumor that might be termed sarcomatoid mesothelioma; and 3) a histologically malignant, keratin-negative, spindle cell tumor that might be termed a sarcoma. Crotty et al. (240) described a case of desmoplastic malignant mesothelioma of the mediastinum, which had been diagnosed as sclerosing mediastinitis by biopsy. In this case, immunostaining for keratin showed strong cytoplasmic positivity in both the sarcomatous cells and the cytologically bland cells within fibrous areas. Flint and Weiss (242) reported that CD34 and keratin expression distinguishes solitary fibrous tumor from desmoplastic mesothelioma. These studies indicate the importance of immunohistochemical staining in the differential diagnosis of fibrous tumors of the pleura, especially for malignant tumors.

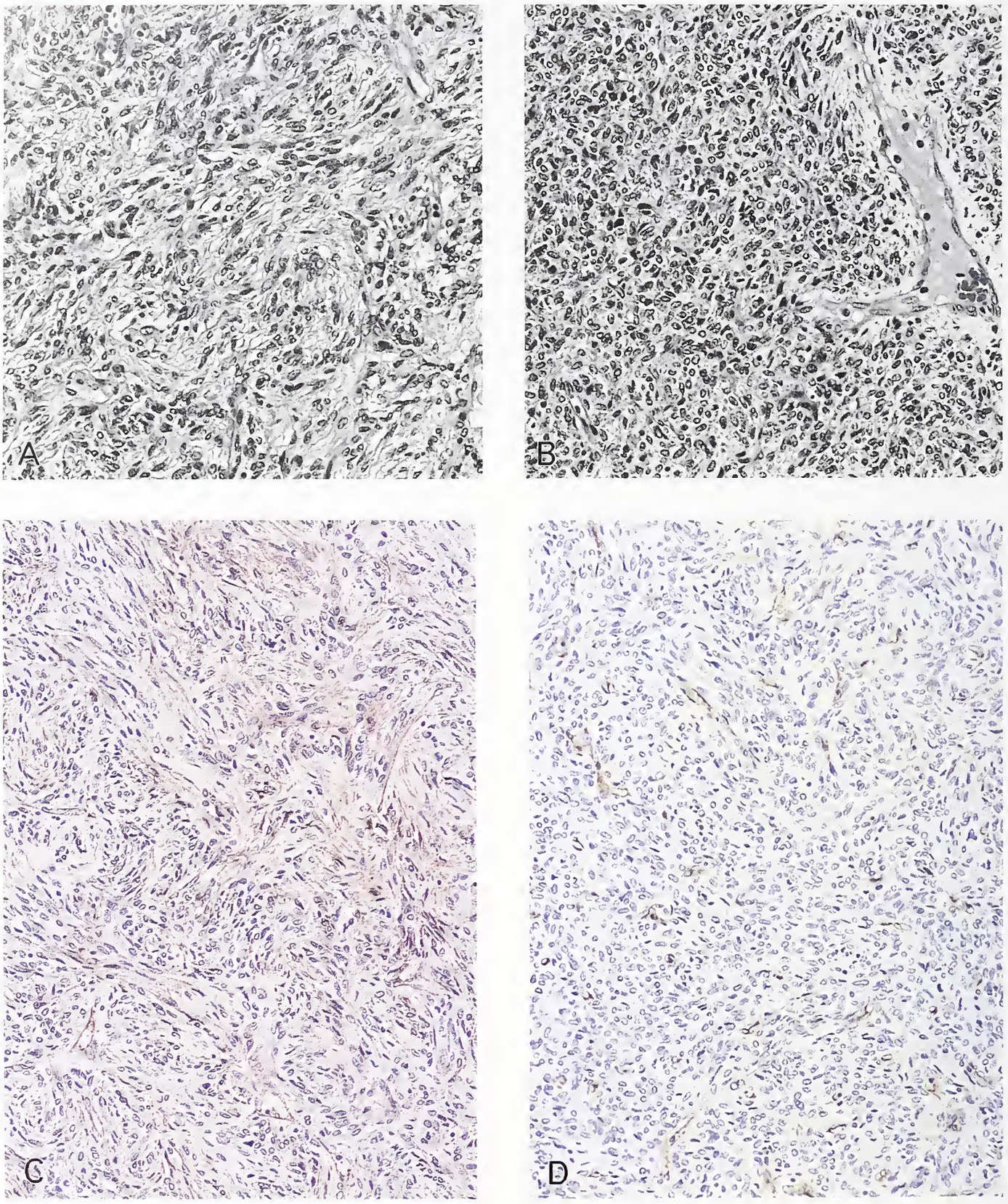


Figure 3-220
LOCALIZED HISTOLOGICALLY MALIGNANT FIBROUS TUMOR OF THE MEDIASTINUM

A: Elongated tumor cells are arranged in interwoven bundles in small areas.

B: In other areas, the tumor is highly cellular and shows diffuse growth of haphazardly arranged short spindle cells with slightly pleomorphic nuclei and scanty cytoplasm with occasional mitotic figures.

C, D: Immunostaining for CD34 displays a positive reaction in tumor cells arranged in interwoven bundles (C) and negative reaction in highly cellular areas, where only vascular endothelial cells are immunostained (D).

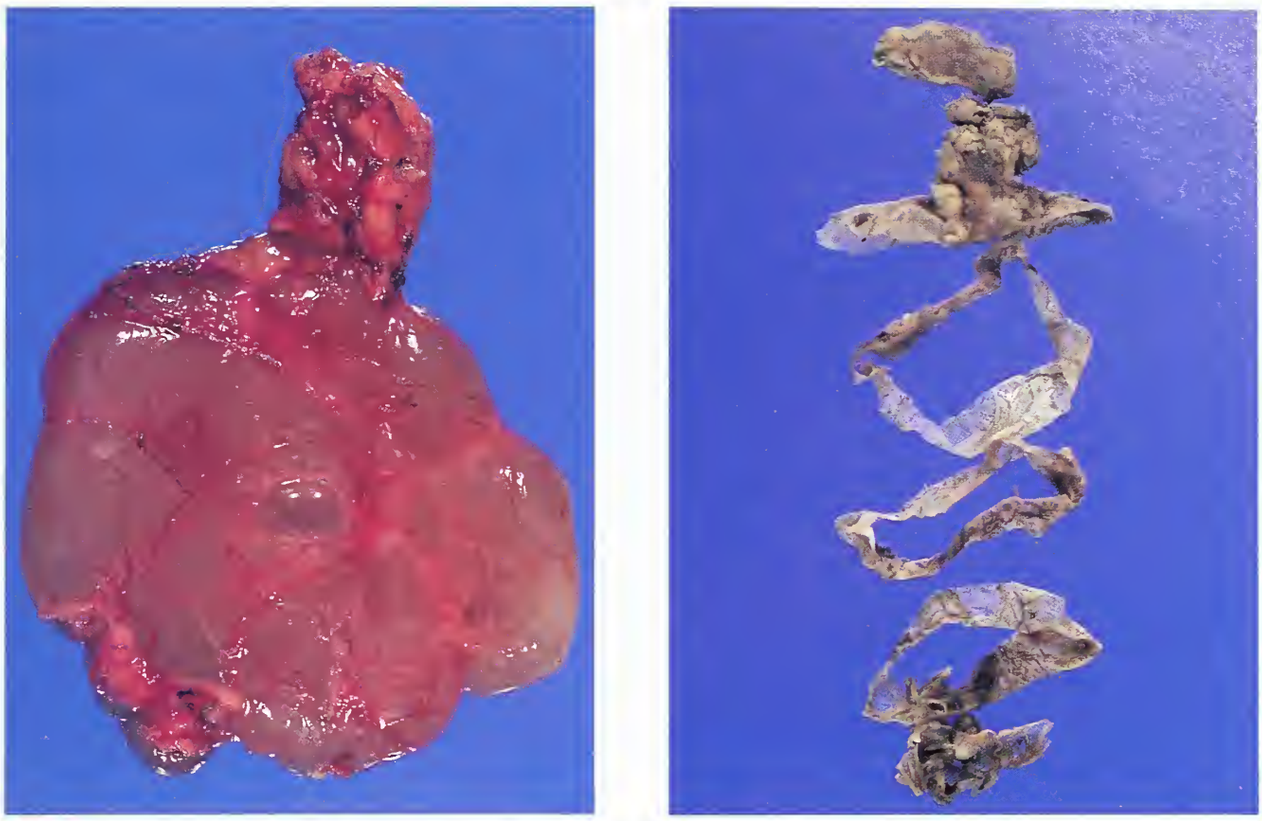


Figure 3-221
THYMIC CYST
Left: A large, thin-walled cyst of the thymus appears multiloculated from outside.
Right: However, it is found to be unilocular.

TUMOR-LIKE LESIONS OF THE THYMUS

Thymic Cyst

Thymic cysts are rare lesions, are most likely congenital and developmental in origin, and are found along the anatomic course of embryologic descent of the thymus from the third pharyngeal pouch, such as the lateral neck from the mandibular angle to the sternal manubrium (247). Thymic cysts derived from an acquired reactive process are rarer than those congenitally formed (254). In our institution, 16 congenital thymic cysts, 5 percent of all mediastinal space occupying lesions, were surgically removed in the past 30 years, during which 79 thymomas were resected (see Table 3-3). There is no sex difference in incidence. Thymic cysts have been seen in the lateral neck of children. In the mediastinum, the cyst is very often asymptomatic, and found by chest X-ray examination in adults; occasionally, symptoms result from compression of surrounding organs or tissue.

Mediastinal cyst is diagnosed by its smooth and sharp contour on chest X ray, and the CT and echography findings. Needle aspiration of the cyst content is also useful for diagnosis.

Grossly, thymic cysts in the neck are tubular and those in the thymus are round or oval. They are uniloculated or multiloculated and thin walled with attached fatty thymic tissue (fig. 3-221). The content is watery clear to straw colored, or chocolate colored due to previous hemorrhage. The lining of an uncomplicated cyst is smooth.

Histologically, the lining is made up of flattened, cuboidal, columnar, ciliated columnar, or stratified squamous epithelium, and may be composed of, or continuous with, thymic tissue (figs. 3-222, 3-223). The epithelial lining may be destroyed by pressure and is replaced by granulation tissue, with or without cholesterol clefts or fibrous tissue (fig. 3-224). It is essential to find thymic tissue in the

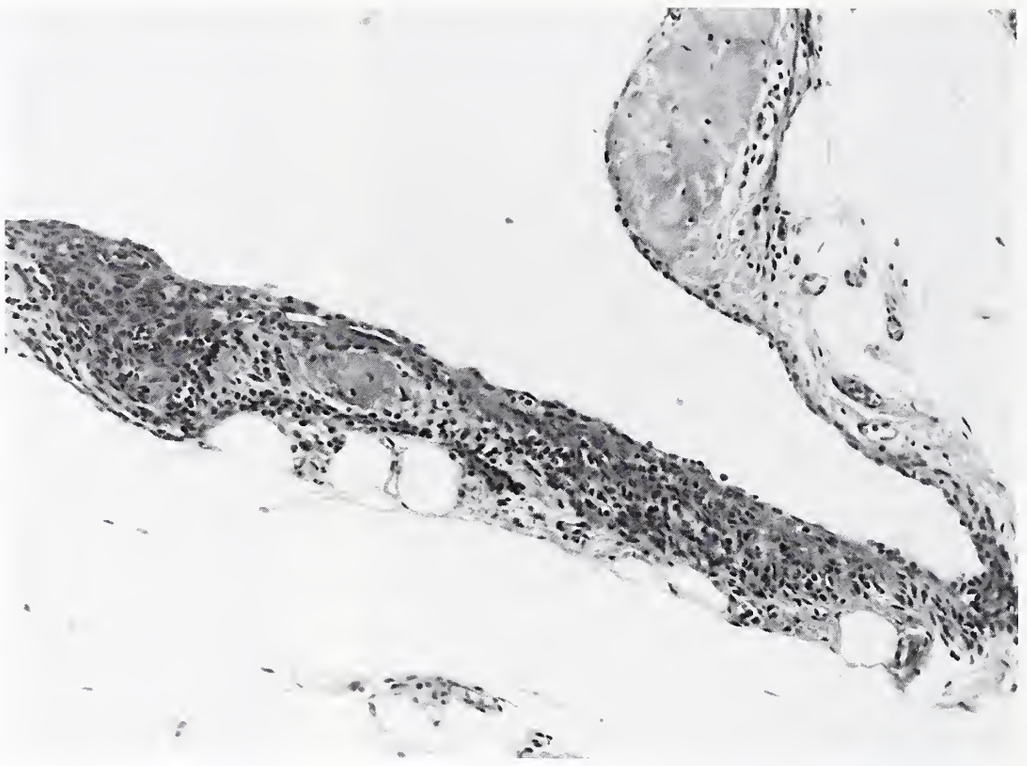


Figure 3-222
THYMIC CYST
The cyst is lined by a single layer of flat cells, which are continuous with atrophic thymic tissue. The wall is collagenous in part. (Figures 3-222 and 3-223 are from the same case.)

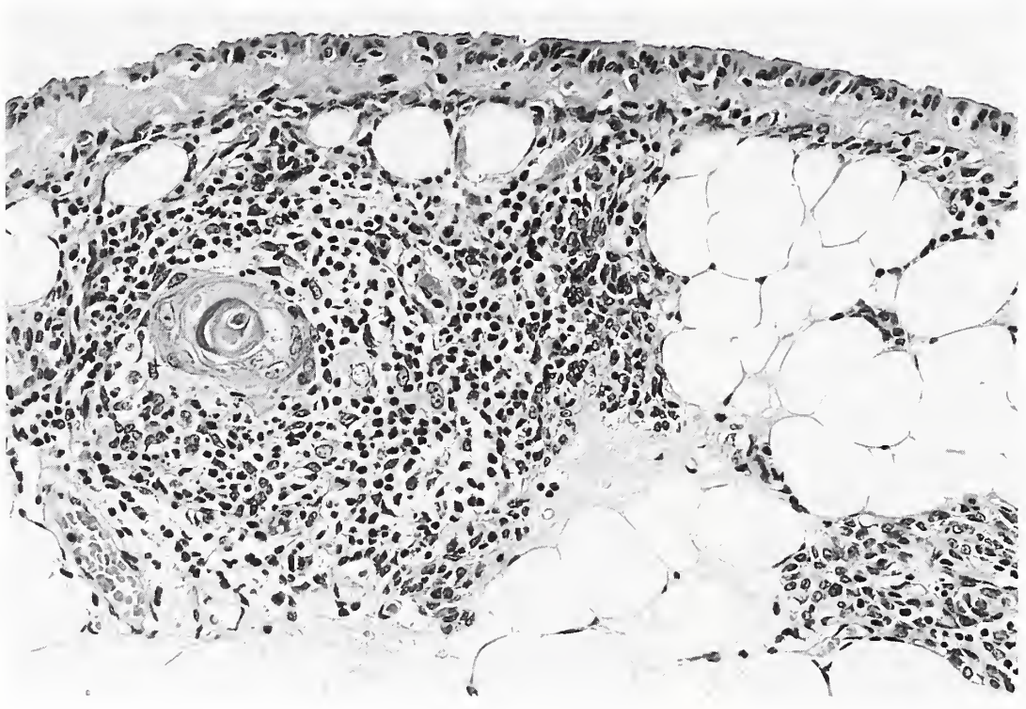


Figure 3-223
THYMIC CYST
The cyst is lined by a single layer of low columnar cells. Thymic tissue with a Hassall corpuscle is attached to the thin-walled cyst. Ciliated columnar cells were found in a small area.

wall of the cyst in order to establish a diagnosis of thymic cyst, and it may be necessary to examine multiple sections of the cyst wall.

The differential diagnosis includes cystic thymoma, cystic teratoma, lymphangioma, and other mediastinal cysts or cystic lesions. Although the above are cystic and may be in the anterior mediastinum, as is thymic cyst, histologic distinction is easy. Even in difficult cases, multiple sectioning of cystic lesions usually leads to a correct diagnosis by disclosure of the characteristic findings of each lesion (250).

Malignant transformation of the epithelial cells of the thymic cyst is rare. Basaloid carcinoma of the thymus may show features suggestive of thymic cyst origin (see Thymic Carcinoma).

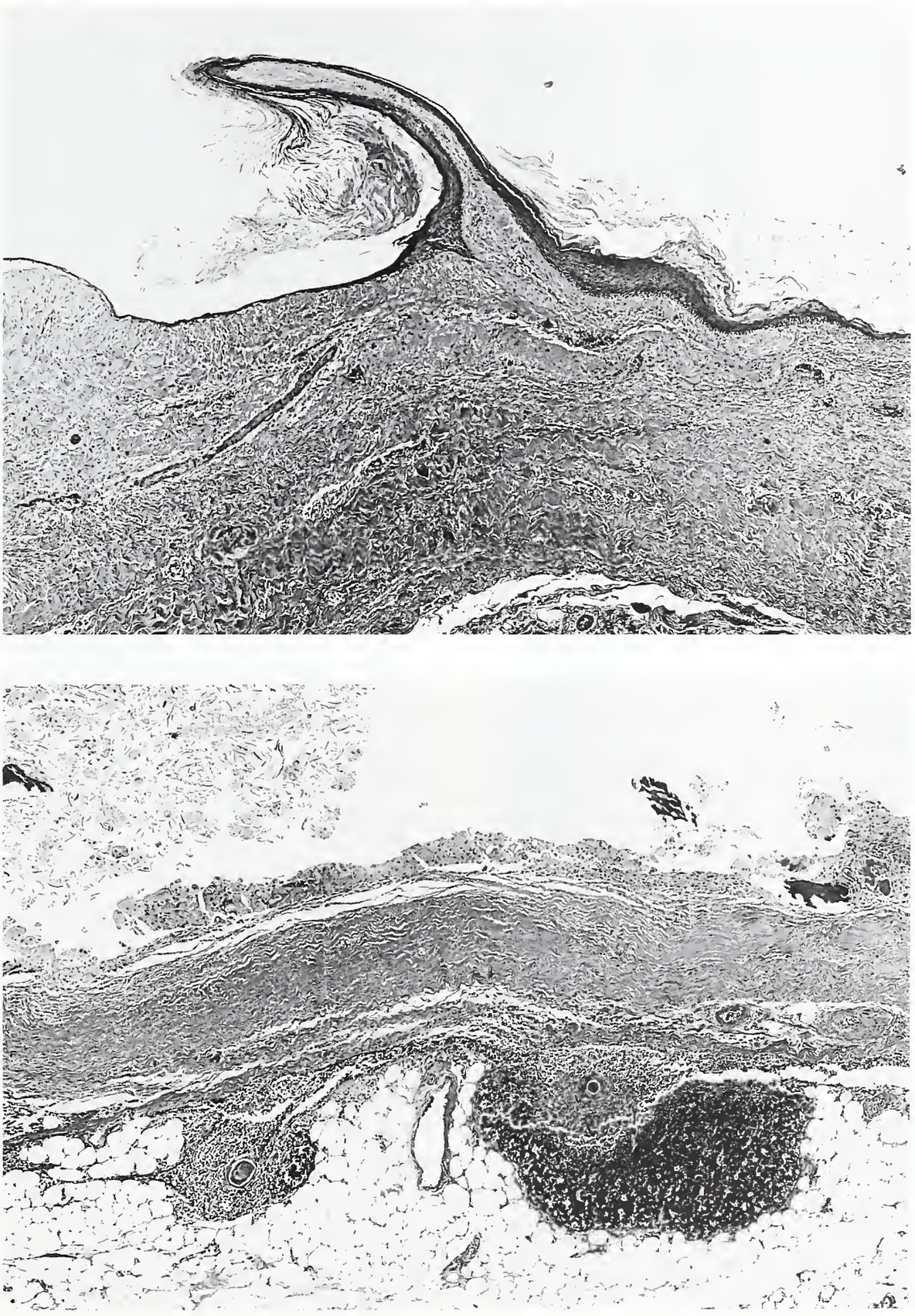


Figure 3-224
THYMIC CYST

Top: The cyst is in part lined by keratotic squamous epithelium. The cyst wall is collagenous.

Bottom: In another area, the lining epithelium has been denuded and replaced by histiocytes. The contents consist of keratotic debris and calcified materials. Thymic tissue with Hassall corpuscles is present outside the cyst.

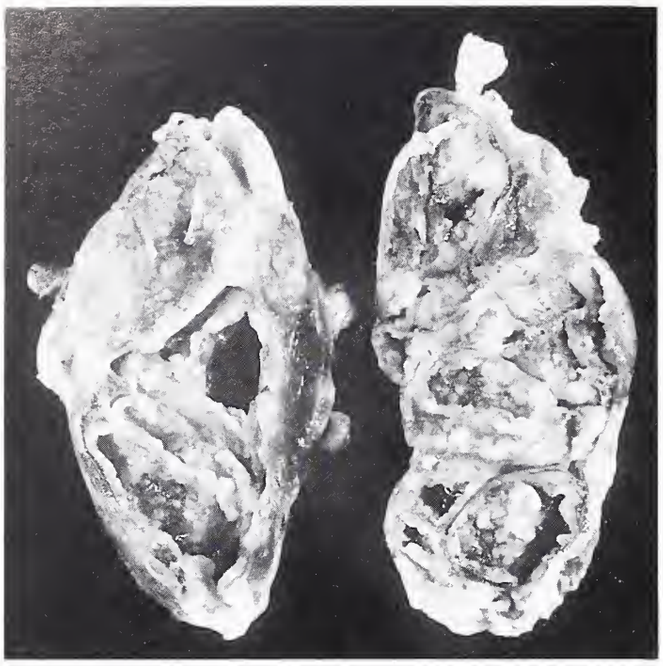


Figure 3-225
ACQUIRED THYMIC CYST
Grossly, this multilocular thymic cyst possesses a fibrous wall of varying thickness. (Fig. 2 from Suster S, Rosai J. Multilocular thymic cyst: an acquired reactive process. Study of 18 cases. Am J Surg Pathol 1991;15:388–98.)

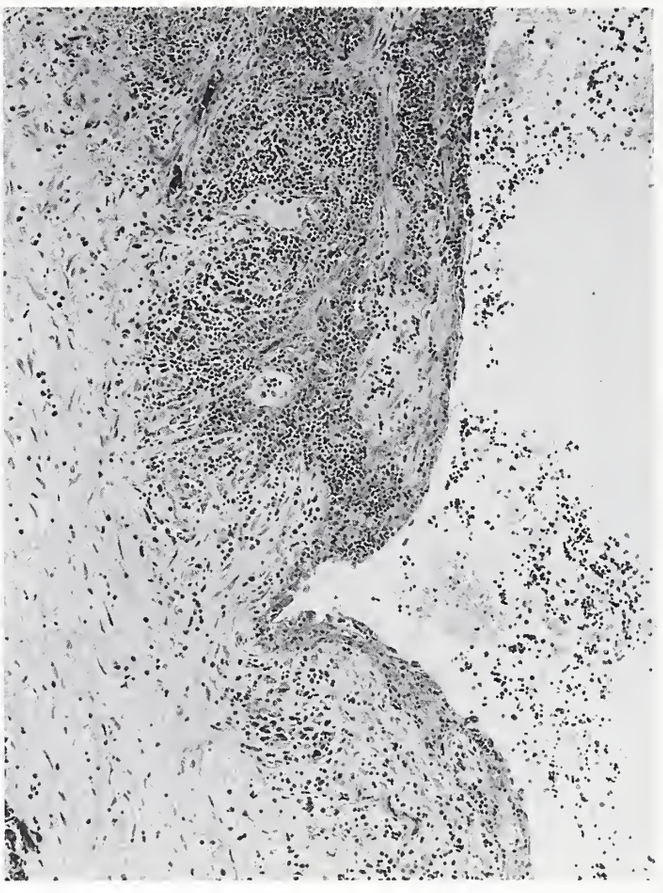


Figure 3-226
ACQUIRED THYMIC CYST
The cyst lining is continuous with thymic lobules in the wall. (Fig. 4 from Suster S, Rosai J. Multilocular thymic cyst: an acquired reactive process. Study of 18 cases. Am J Surg Pathol 1991;15:388–98.)

Well-differentiated papillary squamous cell carcinoma arising from the lining epithelium of a thymic cyst has been reported by Leong and Brown (249).

In 1991, Suster and Rosai (254) reported 18 cases of multilocular thymic cysts related to an acquired reactive process, which was, according to them, "most likely result from cystic transformation of medullary duct epithelium-derived structures (including Hassall corpuscles) induced by an acquired inflammatory process."

Grossly the lesions vary from 3 to 17 cm in greatest dimension. In most cases, they can be enucleated easily, but in some cases they adhere to the surrounding structures making removal difficult. The cut surface shows multiloculated cavities of variegated appearance, filled with dark red blood or brown fluid and areas of recent hemorrhage and fibrosis (fig. 3-225).

Microscopically, multiple cystic cavities are lined in part by squamous, columnar, or cuboidal epithelial cells, often continuous with the islands of non-neoplastic thymic tissue present in the cyst walls. Multilocular cysts are associated with severe acute and chronic inflammation accompanied by fibrovascular proliferation, necrosis, hemorrhage, cholesterol granuloma formation, and reactive lymphoid hyperplasia with prominent germinal centers (figs. 3-226, 3-227). Incidental thymoma and thymic carcinoma were found in two cases each, and similar multilocular cysts were also seen in association with thymic Hodgkin's disease and thymic germinoma (254). Mucosa-associated lymphoid tissue (MALT) lymphoma is also often multicystic (248). The pseudoepitheliomatous hyperplasia in the lining of acquired multilocular thymic cysts noted in some cases is thought to be due to the inflammatory, hemorrhagic, and necrotizing changes often present in these lesions (251,253).

Other Tumor-Like Lesions

Inflammatory or non-neoplastic lesions, both cystic and solid, are rare in the anterior mediastinum. They include tuberculosis, hydatidosis

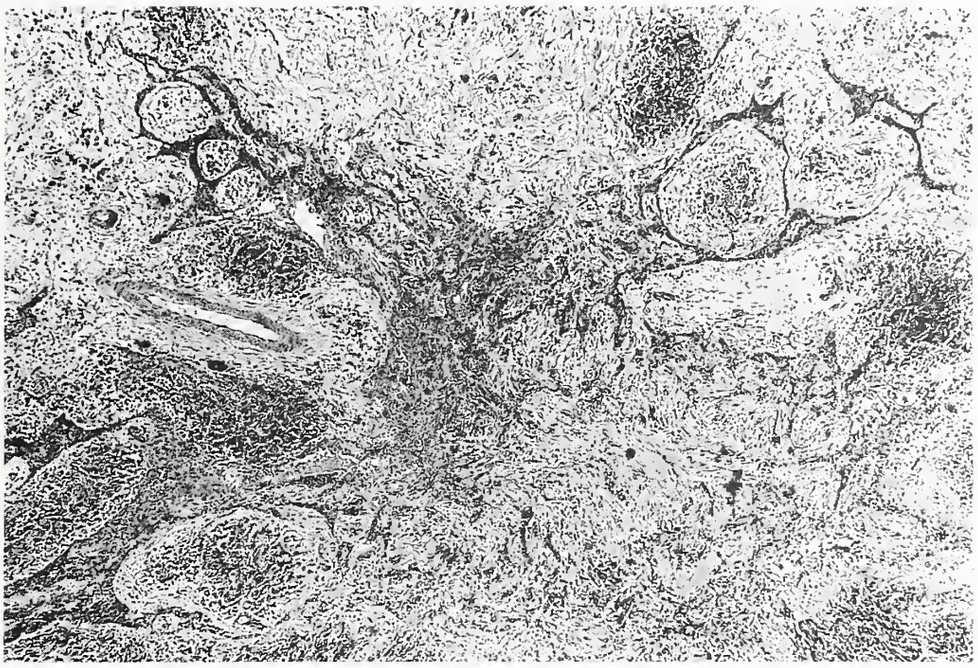


Figure 3-227
ACQUIRED THYMIC CYST
Thymic tissue around the cyst shows elongated, branching strands of thymic epithelium surrounded by fibrous stroma with abundant lymphocytes. (Fig. 5b from Suster S, Rosai J. Multilocular thymic cyst: an acquired reactive process. Study of 18 cases. Am J Surg Pathol 1991;15:388–98.)

(hydatidic cyst) in endemic areas, and inflammatory pseudotumor of unknown etiology, as well as spontaneous thymic hemorrhage and choristoma of the thymus (250,252).

ECTOPIC TISSUES AND TUMORS IN THE ANTEROSUPERIOR MEDIASTINUM

Thyroid Lesions

Thyroid tissue can be found anywhere between the tongue and the aortic arch due to abnormal migration during embryogenesis (257). In the thorax, not only the anterosuperior mediastinum but also the posterior mediastinum may be involved by thyroid lesions, although the former is much more frequent. The majority of mediastinal goiters are substernal extensions of cervical goiter involving the eutopic thyroid gland. Such extension is often seen in the goiter zones. Goitrous lesions arising in ectopic mediastinal thyroid are rare. According to Lindskog and Malm (257), among 1,486 operations for goiter, 46 patients (3.1 percent) showed mediastinal extension of goiter and in 7 patients (0.5 percent) the entire goiter was situated within the thorax without connection to a cervical goiter.

Histologically, thyroid lesions show features of colloid or nodular (adenomatous) goiter or those of a solitary adenoma (figs. 3-228, 3-229). Carcinoma arising in the ectopic thyroid gland

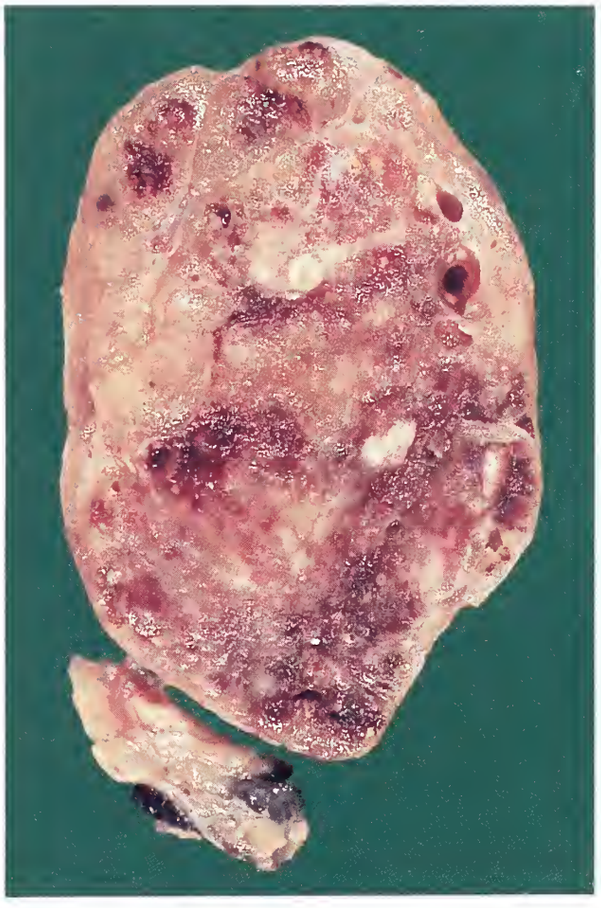


Figure 3-228
MEDIASTINAL GOITER
The cut surface of the roughly oval, encapsulated tumor is nodular, semitranslucent, and brown with areas of hemorrhage, fibrosis, and microcystic degeneration. There was no connection with the thyroid gland of the neck.

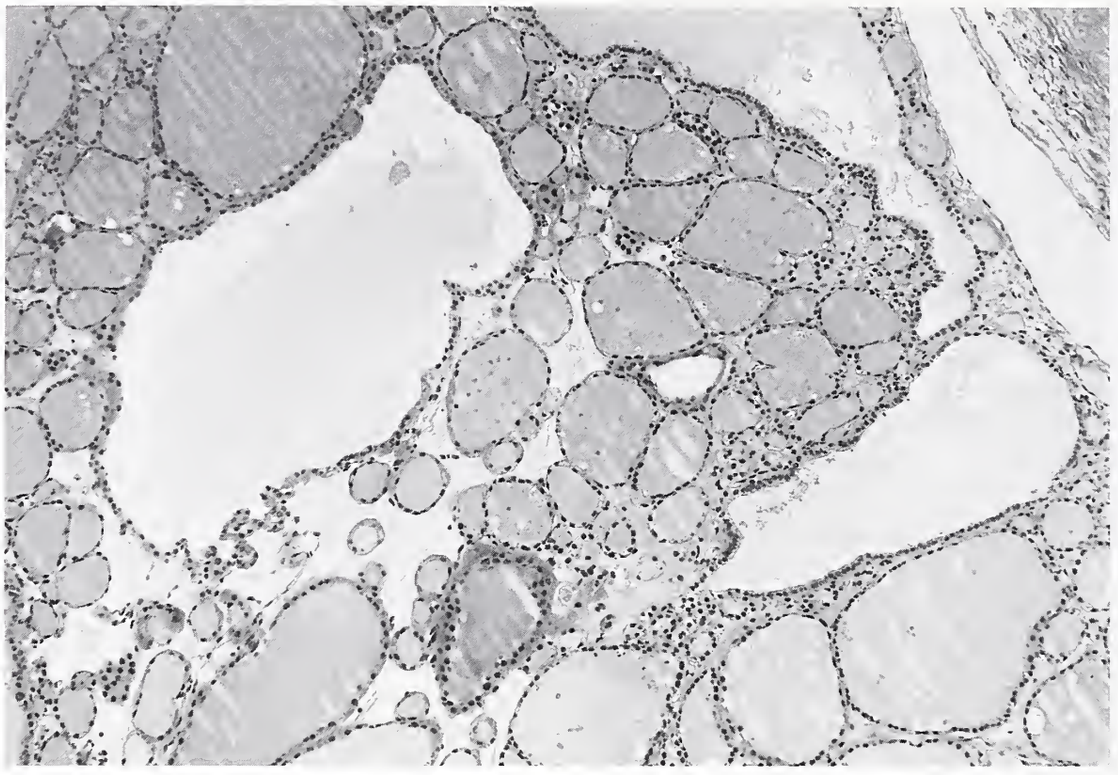


Figure 3-229
MEDIASTINAL GOITER
Follicles vary in size, tending to be large, and are lined by flat epithelium containing thin colloid.

is extremely rare. For a detailed gross and microscopic description of such lesions, the reader is referred to the Atlas of Tumor Pathology, "Tumors of the Thyroid Gland" (259).

Parathyroid Lesions

Because of the likely common origin of the thymus and the inferior parathyroid glands from the third branchial pouch, ectopic parathyroid gland may be found in the anterosuperior mediastinum adjacent to, or within, the thymus (fig. 3-230). Mediastinal parathyroid tumors were found in 64 (22 percent) of 285 patients who underwent surgery for hyperparathyroidism, and in 20 (38 percent) of 53 patients requiring repeat surgery for persistent or recurrent hyperparathyroidism (255). Of these parathyroid tumors, 52 were situated in the anterior mediastinum and 12 in the posterior mediastinum. For clinical signs, diagnostic approaches, and gross and histologic findings of mediastinal parathyroid lesions, readers are referred to Atlas of Tumor Pathology, "Tumors of the Parathyroid Gland" (256).

The following is an illustrative case of a parathyroid lesion in the mediastinum. The patient, a 29-year-old female, had three parathyroid glands (bilateral upper and left lower) removed and a brown tumor of the femur curetted because of hyperparathyroidism. The three parathyroid glands were reported to be normal and slightly hyperplastic. Since hypercalcemia persisted postoperatively, right thyroid lobectomy and dissection of the superior mediastinum were done 6 months later, but no parathyroid gland was found. Approximately 1 year later, a ^{201}T1 scintigram revealed uptake in the anterosuperior mediastinum and the patient underwent removal of a 2.2 x 1.5 cm tumor located in the superior portion of the right lobe of the thymus. The tumor was well defined but showed possible invasive growth. Histologically, it consisted of trabeculae, small follicles, and tubules consisting of small polygonal cells with or without clear cytoplasm and a few small groups of oncocytic cells (fig. 3-231). The postoperative course was uneventful.

A very rare nonsecretory parathyroid carcinoma arising in the anterosuperior mediastinum was reported by Murphy et al. (258).

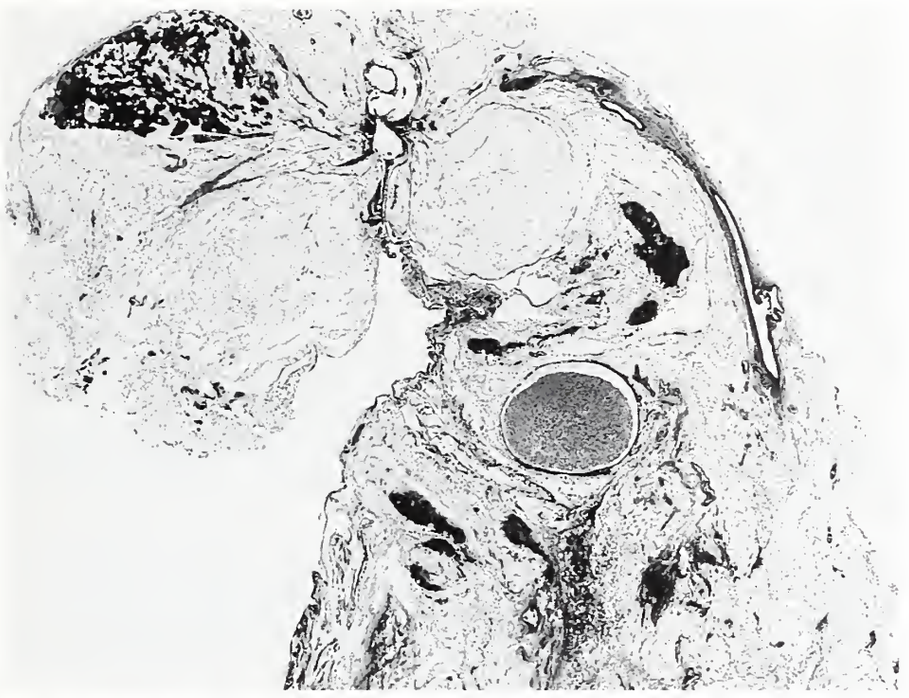


Figure 3-230
MEDIASTINAL
PARATHYROID GLAND

A parathyroid gland of normal size and appearance is seen in the left upper corner of the photograph and microcystic change is seen in the thymus.

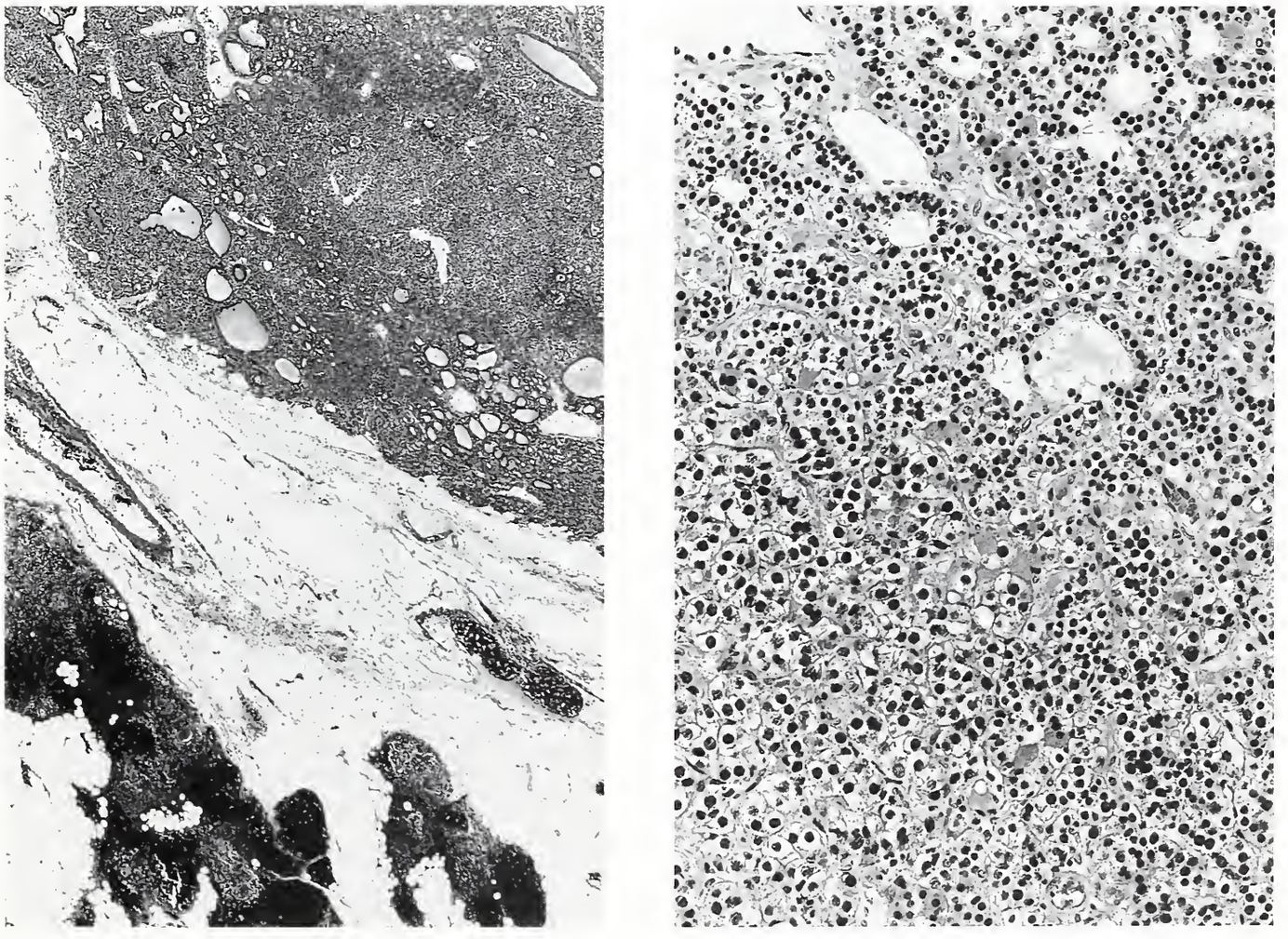


Figure 3-231
MEDIASTINAL INTRATHYMIC PARATHYROID ADENOMA

Parathyroid adenoma, which is composed of sheets, nests, trabeculae, tubules, and follicles made up of chief cells, a few water-clear cells, and small clusters of oncocytic cells, is bordered by thymic tissue. (Left: low-power view; right: high-power view.)

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4

TUMORS OF THE MEDIASTINUM EXCLUDING THE THYMUS, HEART, AND GREAT VESSELS

MESENCHYMAL TUMORS

Mesenchymal tumors, either benign or malignant, are rare in the mediastinum, constituting less than 2 percent of mediastinal tumors and tumor-like lesions (see Table 3-3). Many types of tumors have been reported (Table 4-1) but symptoms and signs are similar to those of other benign and malignant mediastinal tumors, and not specific for mediastinal mesenchymal tumors. Pathologic features are similar to similarly named tumors of the soft tissue occurring at other sites. Readers should refer for details to the related atlas and monographs (4,5,7).

Benign Mesenchymal Tumors and Tumor-like Lesions

Lymphangioma is a benign tumor of either neoplastic or hamartomatous nature composed of proliferating lymphatic vessels lined by endothelial cells. Interconnecting vessels contain chylous material and vary in size, grossly appearing cystic or spongy. Lymphangioma occurs in any compartment of the mediastinum but is most frequent in the anterosuperior mediastinum. In children, *cystic hygroma* of the neck may extend into the mediastinum. Histologically, it resembles hemangioma, and may contain

Table 4-1

MESENCHYMAL TUMORS OF THE MEDIASTINUM*

Tumors of lymph vessels
- Lymphangioma
- Lymphangiomatosis
- Lymphangiomyoma

Tumors of blood vessel origin
- Hemangioma
- Hemangioendothelioma
- Hemangiomatosis
- Epithelioid hemangioendothelioma
- Malignant hemangioendothelioma (angiosarcoma)

Tumors of pericyte origin
- Hemangiopericytoma

Tumors and tumor-like fibrohistiocytic lesions
- Fibromatosis
- Fibrosarcoma
- Malignant fibrous histiocytoma

Tumors of adipose tissue
- Lipoma
- Lipomatosis
- Lipoblastomatosis
- Liposarcoma

Tumors of muscle origin
- Rhabdomyoma
- Rhabdomyosarcoma
- Leiomyoma
- Leiomyosarcoma

Tumors of pluripotential mesenchyme
- Benign mesenchymoma
- Malignant mesenchymoma
- Synovial sarcoma

Tumors of skeletal tissues
- Chondroma
- Osteogenic sarcoma
- Chondrosarcoma

Other tumors and tumor-like conditions
- Solitary fibrous tumor (fibrous mesothelioma)
- Myxoma
- Meningioma
- Chordoma
- Granular cell tumor
- Extramedullary hematopoiesis
- Histiocytosis X
- Amyloid tumor

*From reference 7.

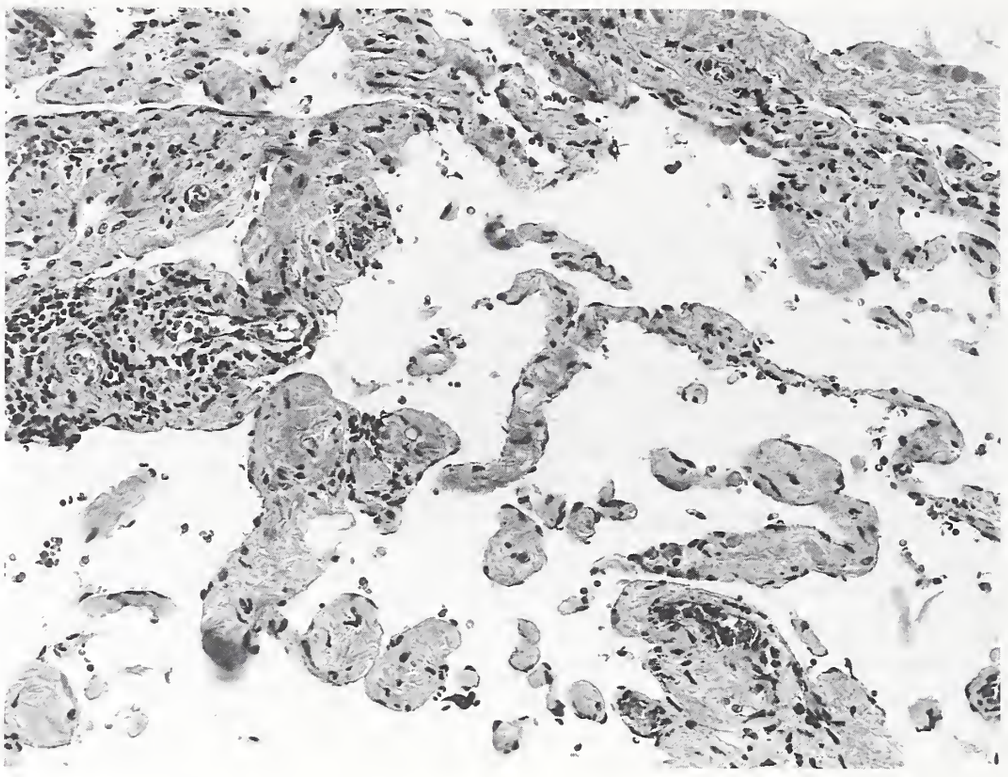


Figure 4-1
LYMPHANGIOMA

Histology of a spongy tumor somewhat resembles emphysematous lung. It consists of interconnecting channels lined by flat endothelial cells. The wall is variably fibrotic and focally infiltrated by lymphocytes.

Figure 4-2
LYMPHANGIOMA

A cystic lymphangioma is lined by flat endothelial cells, beneath which are bundles of smooth muscle.

smooth muscle fibers. Lymphocytic infiltration is frequently noted in the interstitium and contents are not bloody unless hemorrhage occurs (figs. 4-1, 4-2). Factor VIII–related protein cannot be demonstrated immunohistochemically.

Lymphangiomatosis is a systemic disorder in children, and *lymphangiomyomatosis* involves the lung parenchyma and mediastinal lymph nodes of young women.

Hemangioma is subdivided into capillary, cavernous, and venous types by the size and structure of blood vessels, as in hemangiomas at other locations. In the mediastinum cavernous hemangiomas (fig. 4-3) are more common than other types. Despite a frequently large size, an often infiltrating appearance, and sporadic mitotic activity, follow-up studies demonstrate the benign nature of mediastinal hemangiomas (8).

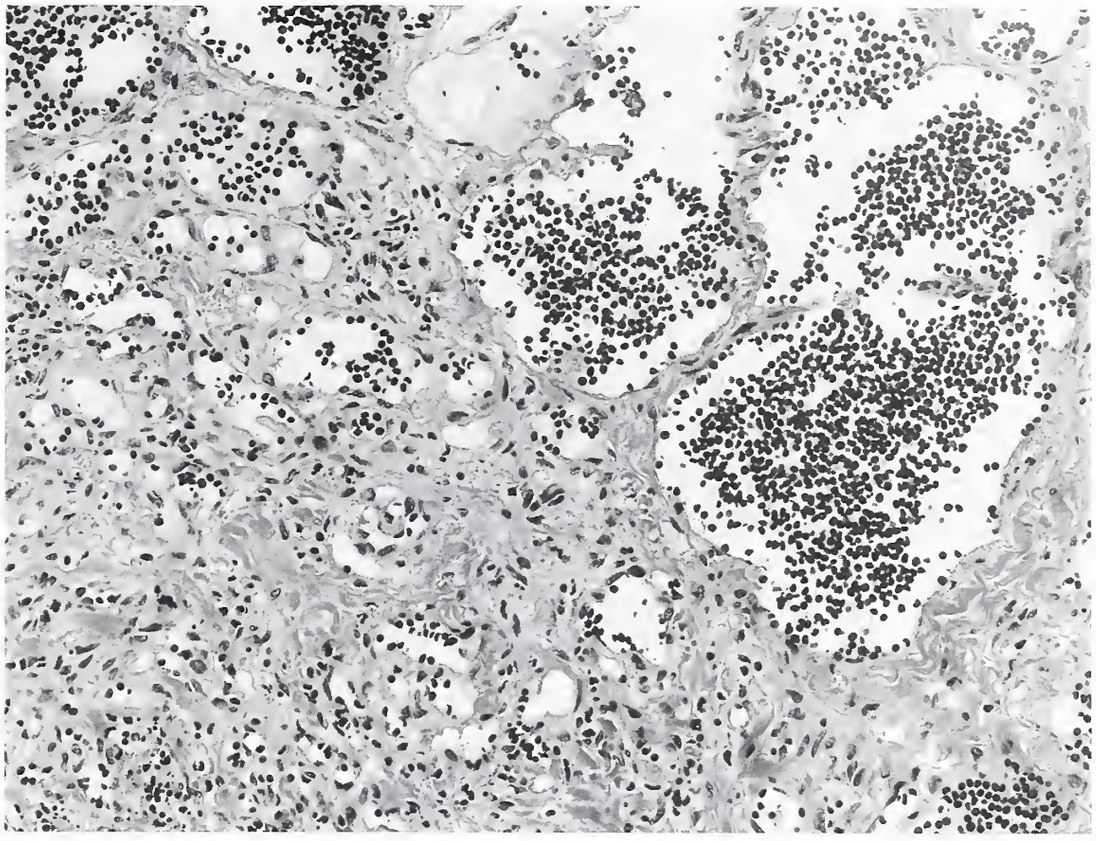
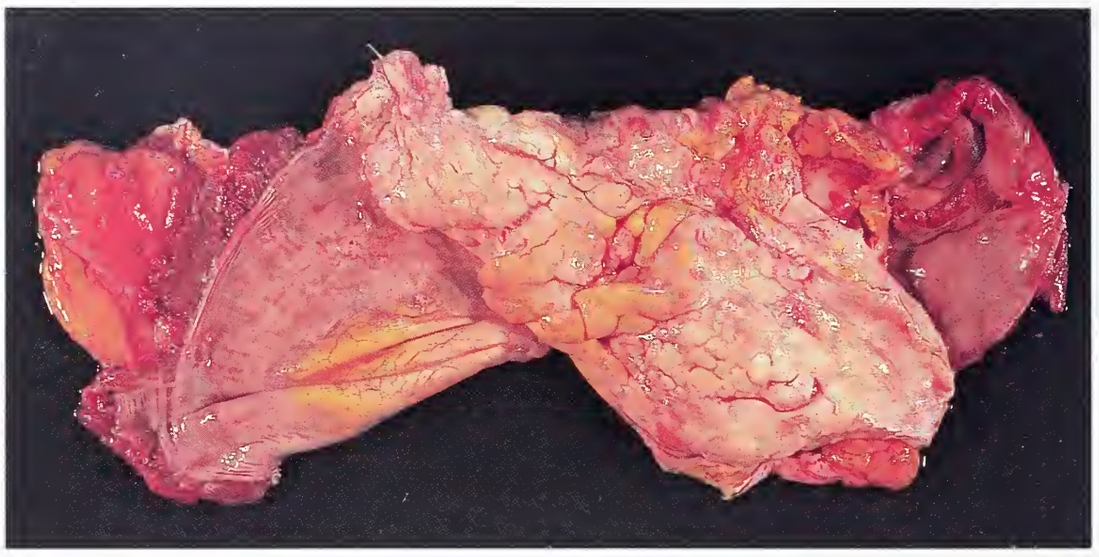


Figure 4-3
CAVERNOUS HEMANGIOMA

The tumor consists of variously sized lumina containing blood and lined by flat endothelial cells. The walls are fibrous. It was 1.7 x 1.4 x 1.0 cm and was located in the posterior mediastinum.

Fibromatosis rarely involves the mediastinum. Although we have not seen any cases of fibromatosis, two cases possessing some features suggestive of mediastinal fibromatosis were encountered. One case was a 23-year-old female student who developed extensive fibrosis of the anterior and middle mediastinum extending into the right upper lobe of the lung, left main bronchus, pericardium, epicardium, and diaphragm; the patient died of respiratory failure after 6 years of therapy (fig. 4-4, top). An unusual feature in this case was the extensive hyalinization of the lesion recognized at autopsy, which may have been due to radiotherapy. There were no epithelioid granulomatous lesions but scant chronic inflammatory cells were seen around blood vessels (fig. 4-4, bottom). No fungi were demonstrated. These findings probably indicate end-stage mediastinal fibrosis (fibrous or sclerosing mediastinitis, granulomatous mediastinitis) of unknown etiology (3,10). The other case was fibromatosis (desmoid) in a 71-year-old man. The primary site in this case was probably the right chest wall, rather than the mediastinum, involving the 1st to 4th ribs, and extending into the mediastinum and neck. The patient has been free of recurrence for 5 years after repeated surgical removal and radiotherapy extending over a 3.5-year period. Histology showed a typical desmoid tumor with fibroblastic proliferation, collagenization, and slit-like vessel proliferations (fig. 4-5).

Other benign mesenchymal tumors include *lipoma, chondroma, granular cell tumor,* and *rhabdomyoma.* The last should be differentiated from rhabdomyomatous thymoma (see fig. 3-73). *Hemangiopericytoma* is either benign or malignant. Occurrence of true hemangiopericytoma in the mediastinum is extremely rare (4). If the histology of a mediastinal tumor is suggestive of hemangiopericytoma, the tumor should be thoroughly examined in order not to overlook features characteristic of thymoma, since a hemangiopericytoma-like thymoma is more common.



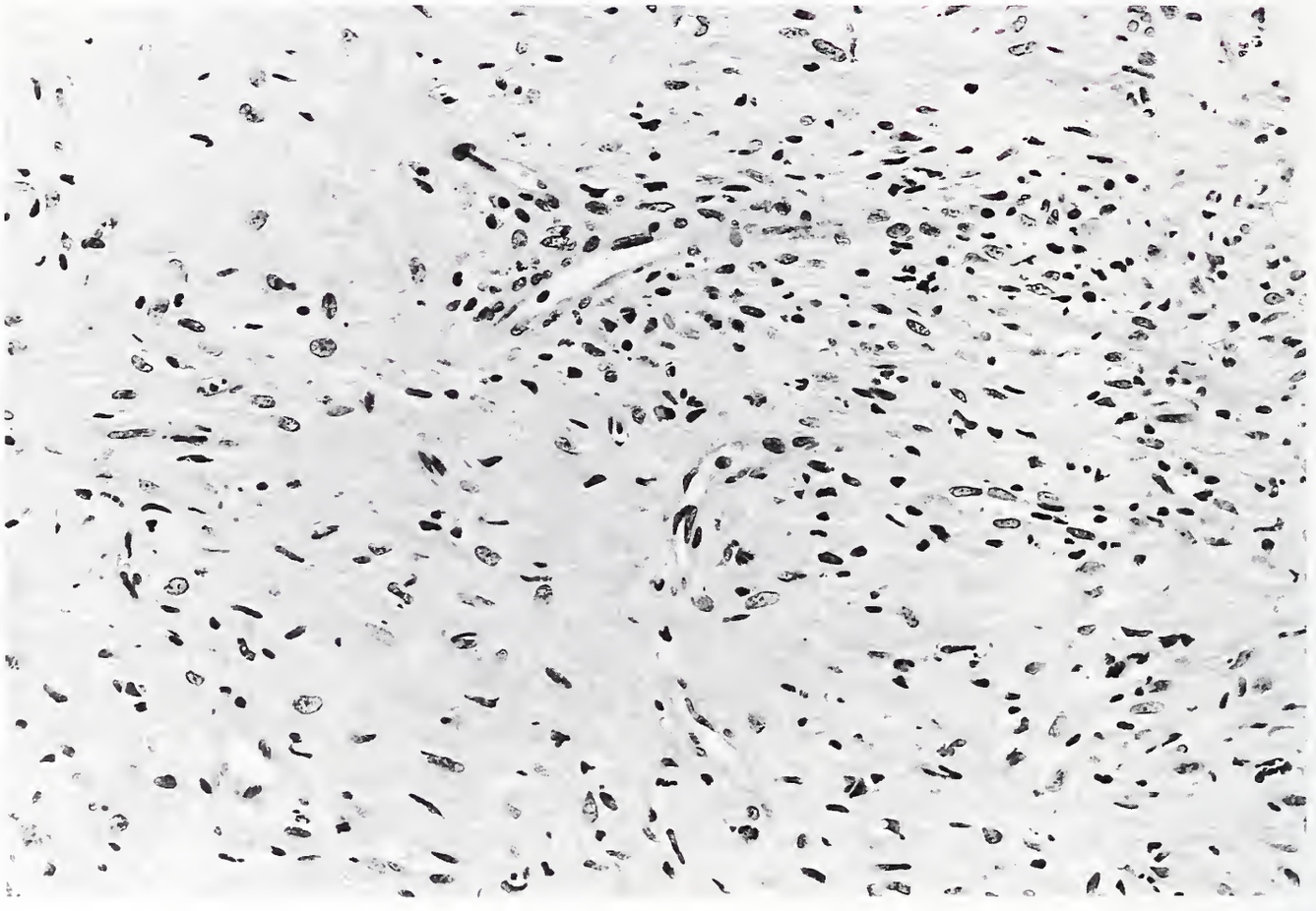


Figure 4-4
MEDIASTINAL FIBROSIS

Top: A plate-like fibrous tumor with a nodular surface is attached to the anterior portion of the diaphragm. It involved the lung, bronchi, pericardium, and epicardium.

Bottom: A needle biopsy of the tumor discloses proliferation of fibroblasts with collagenization and a mild degree of inflammatory cell reaction around slit-like blood vessels.

Figure 4-5
FIBROMATOSIS INVOLVING CHEST WALL AND MEDIASTINUM
Proliferation of fibroblasts with a mild degree of collagenization is associated with proliferation of slit-like blood vessels.

Malignant Mesenchymal Tumors

We have seen one case each of *angiosarcoma* (*malignant hemangioendothelioma*), *malignant fibrous histiocytoma, mesenchymal chondrosarcoma,* and *liposarcoma* of the mediastinum (2,6,9). A large liposarcoma, 17 x 9 x 6 cm, was incompletely removed from a 71-year-old male, who had complained of hoarseness for 2 years. It was situated in the superoanterior mediastinum extending into the right supraclavicular fossa. Histologically, it consisted in part of tumor with features of well-differentiated liposarcoma and in part of tumor with a malignant fibrous histiocytoma-like growth pattern, in which the lipomatous nature could still be recognized (fig. 4-6). Lipoma and liposarcoma also arise from the thymus.

Recently, Witkin et al. (13) reported four cases of a biphasic tumor of the mediastinum with features of *synovial sarcoma* (figs. 4-7, 4-8). The tumors were located in the superior and middle compartments of the mediastinum, and frequently adhered to the pericardium or pleura but did not appear to arise from a mesothelial surface. Three patients who were followed clinically died of the tumor within 4 years of diagnosis. The tumor is considered to originate from pluripotential mesenchyme and should be distinguished from biphasic mesothelioma, thymoma with glandular features (see fig. 3-62), and malignant peripheral nerve sheath tumor with glandular differentiation.

Suster et al. (12) reported four *rhabdomyosarcomas,* unassociated with germ cell teratomatous or thymic carcinomatous components, in young adults (three men and one woman of 19 to 27 years of age). Histologically, two tumors were alveolar rhabdomyosarcomas, one was an embryonal rhabdomyosarcoma, and the remaining one was a pleomorphic rhabdomyosarcoma. All tumors were highly aggressive, and recurrence and metastases developed within the first 6 months after diagnosis. A case of rhabdomyosarcoma with glycogen-rich clear cells was reported by Bégin et al. (1). This entity should be differentiated from more commonly encountered clear cell tumors seen in the mediastinum.

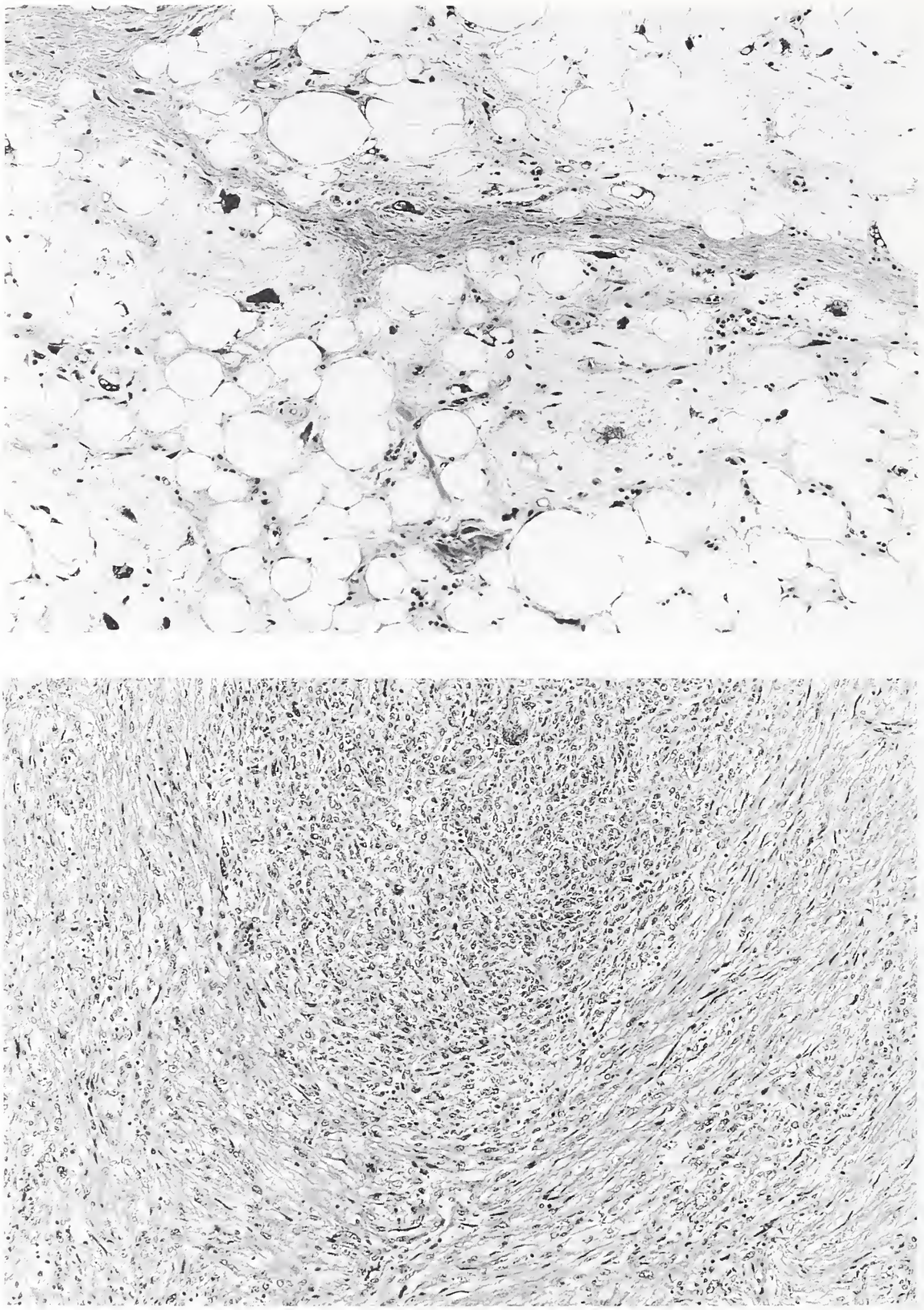


Figure 4-6
LIPOSARCOMA

Top. The tumor consists in part of mature fat cells and scattered lipoblasts with bizarre nuclei with focal myxoid matrix.
Bottom. In other areas, the tumor is cellular and consists of bundles of elongated cells with moderately atypical nuclei. However, fatty droplets can still be seen in the cytoplasm at higher magnification.

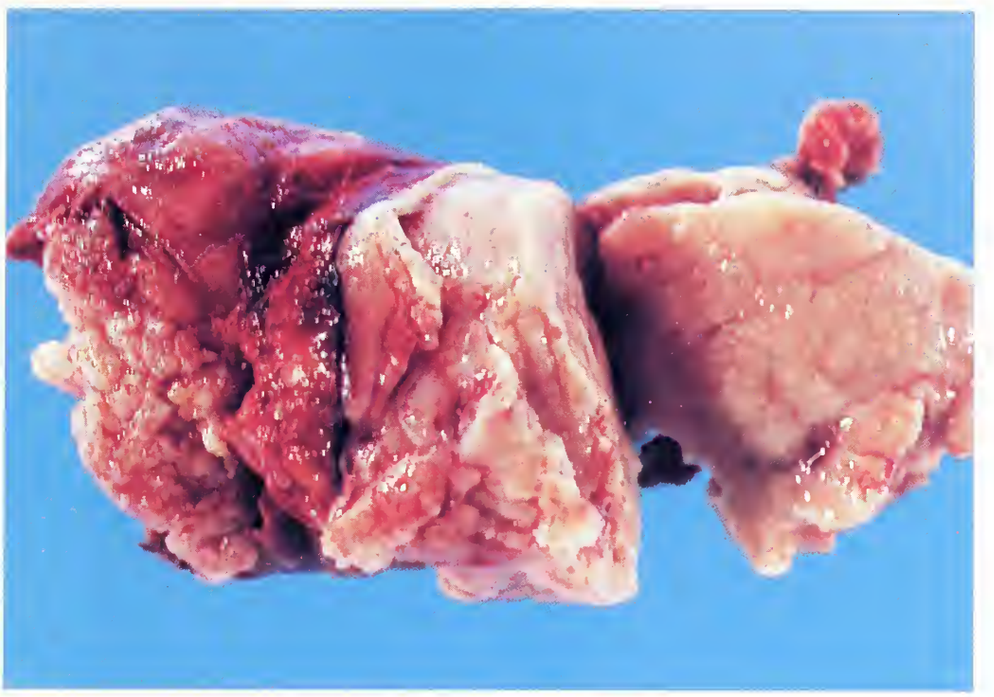


Figure 4-7
BIPHASIC TUMOR WITH FEATURES OF SYNOVIAL SARCOMA

External and cut surfaces of the tumor, which is tan and friable. (Fig. 1 from Witkin GB, Miettinen M, Rosai J. A biphasic tumor of the mediastinum with features of synovial sarcoma: a report of four cases. Am J Surg Pathol 1989;3:490–9.)

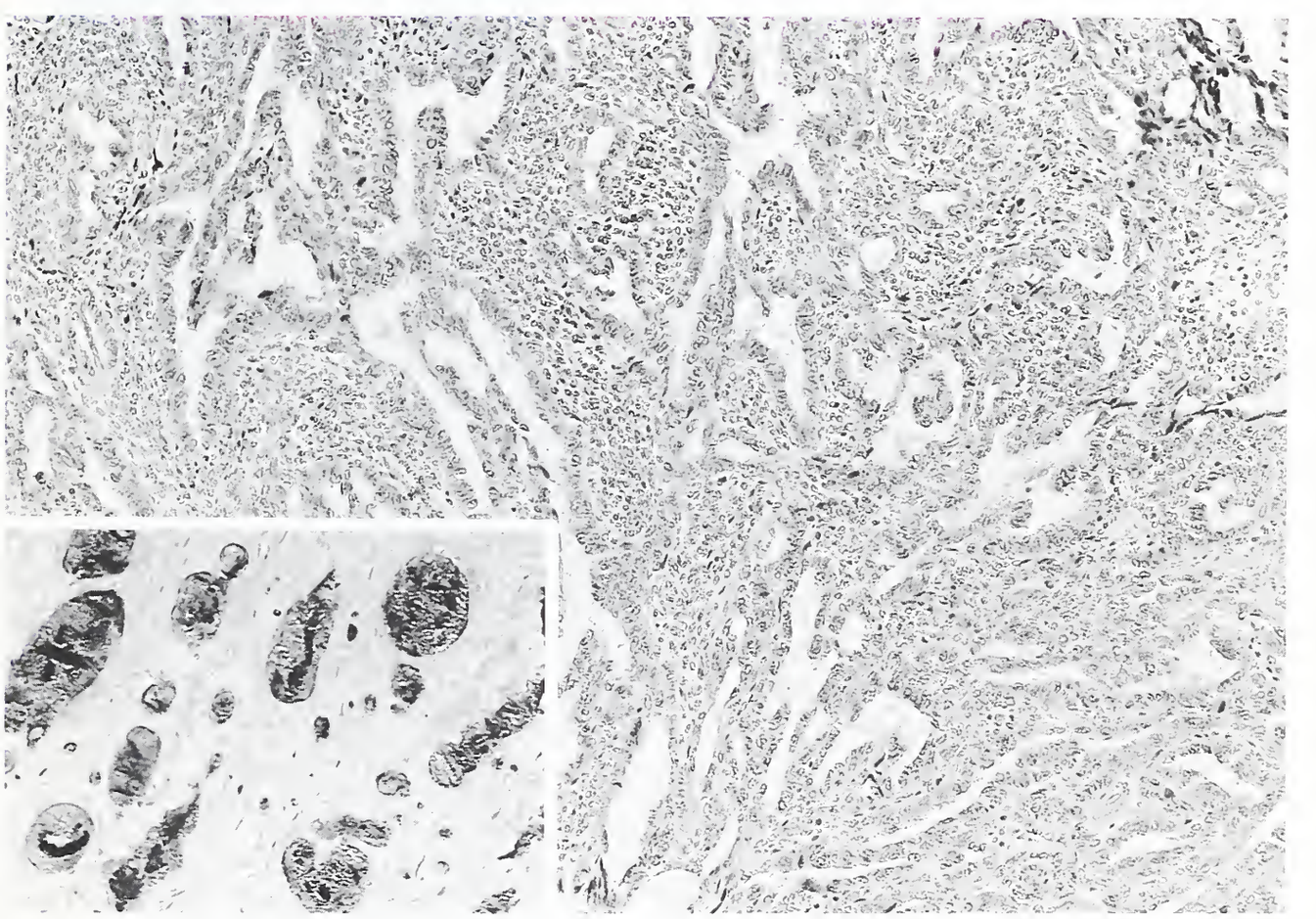


Figure 4-8
BIPHASIC TUMOR WITH FEATURES OF SYNOVIAL SARCOMA

Glandular spaces and clefts are intermixed with a monomorphic plump to spindled sarcomatous component. Inset: PAS-positive, diastase-resistant material in glandular lumina. (Fig. 3 from Witkin GB, Miettinen M, Rosai J. A biphasic tumor of the mediastinum with features of synovial sarcoma: a report of four cases. Am J Surg Pathol 1989;3:490–9.)

Suster et al. (11) described 12 patients with *epithelioid hemangioendothelioma* of the anterior mediastinum: three women and nine men, aged 19 to 62 years. The tumors were either encapsulated or locally infiltrative. Some displayed the histologic features of classic low-grade epithelioid hemangioendothelioma seen at other locations and others showed increased cellular atypia and mitotic activity. Five patients developed metaplastic bone formation and osteoclast-type giant cells, and four tumors displayed a prominent intravascular papillary endothelial component in areas. However, the authors concluded that "despite their ominous clinical radiological and pathological features, epithelioid hemangioendotheliomas of the anterior mediastinum appear to behave as low-grade malignant neoplasms that may be adequately controlled in most instances by surgery alone."

NEUROGENIC TUMORS AND TUMORS OF PARAGANGLIA

According to Marchevsky and Kaneko (22), neurogenic tumors account for 19 to 39 percent of mediastinal tumors. They occur most frequently in the posterior mediastinum, arising from sympathetic ganglia, paraganglia, and peripheral nerves. A variety of neurogenic tumors, both benign and malignant as seen in other parts of the body, occur in the mediastinum, particularly the posterior mediastinum. Concerning clinical findings, gross and microscopic features, and the outcome of tumors in detail, textbooks, monographs, and atlases on tumors of the peripheral nerves and ganglia should be consulted (16,20,22).

Among neurogenic tumors, *schwannoma (neurilemmoma, neurinoma)* is the most frequent in the mediastinum. It is connected with a peripheral nerve, and is single in most cases. Multiple schwannomas are often associated with von Recklinghausen's disease. Patients with schwannoma are asymptomatic in most cases and the tumor is generally found incidentally on chest X-ray examination, but may cause symptoms due to compression of nearby organs by a large tumor. The tumor is spherical to oval and encapsulated. The cut surface is milky white or pale yellow, homogeneous, and partly myxomatous or cystic (fig. 4-9). Histologically, diagnosis can usually be established with ease, but in longstanding tumors it may be difficult to find the characteristic features of Antoni type A and B due to extensive degenerative changes; scanty tumor tissue of viable appearance and dilated vessels with a hyalinized wall point to a correct diagnosis (figs. 4-10, 4-11).

Figure 4-9
SCHWANNOMA
The outer and cut surfaces of a roughly spherical tumor are shown, revealing encapsulation and central microcystic degeneration.

Malignant transformation is almost nonexistent and thus patients can be observed clinically even when the tumor is incompletely removed because of its particular location, such as near nerve roots.

Melanocytic schwannoma is a rare pigmented variant. It may be dumbbell shaped and extend from the posterior mediastinum to the spinal canal. A common origin of Schwann cells and melanocytes from the neural crest would explain this variety.

Neurofibroma is second to schwannoma in frequency, and presents as a single tumor or multiple tumors (as in neurofibromatosis associated with von Recklinghausen's disease). It grows within the nerve and frequently is fusiform in shape. In contrast to schwannoma, it is

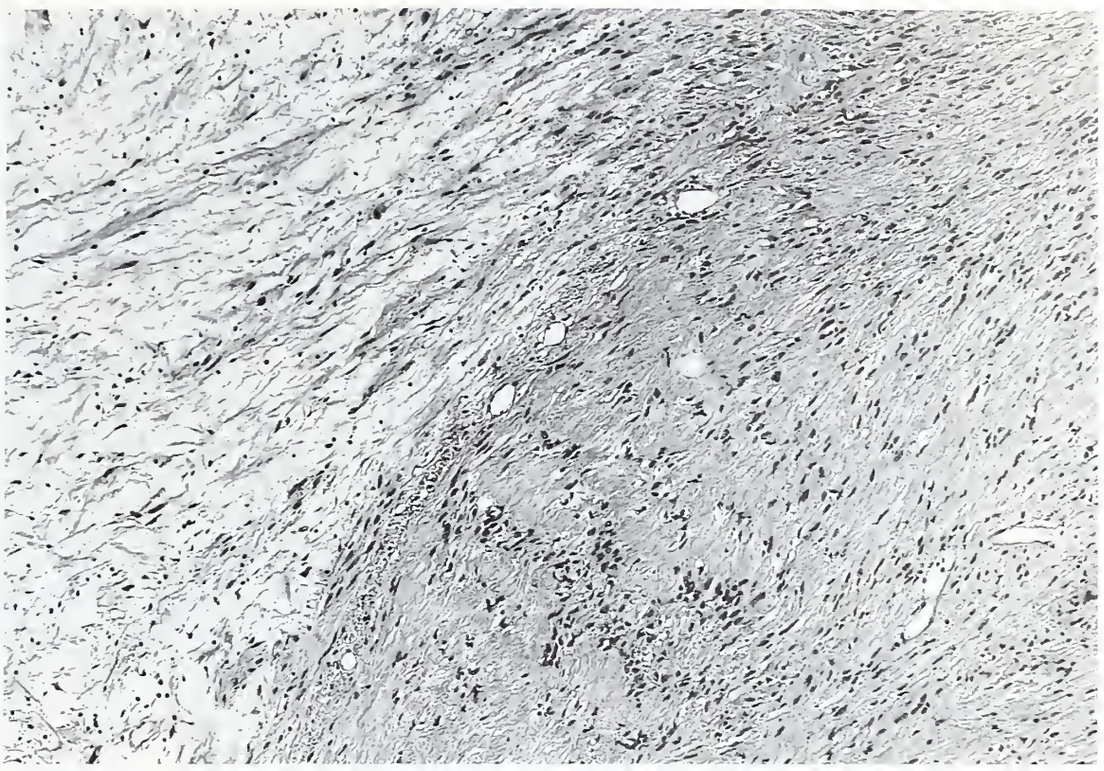


Figure 4-10
SCHWANNOMA
Histology of Antoni type A on the right and B on the left.

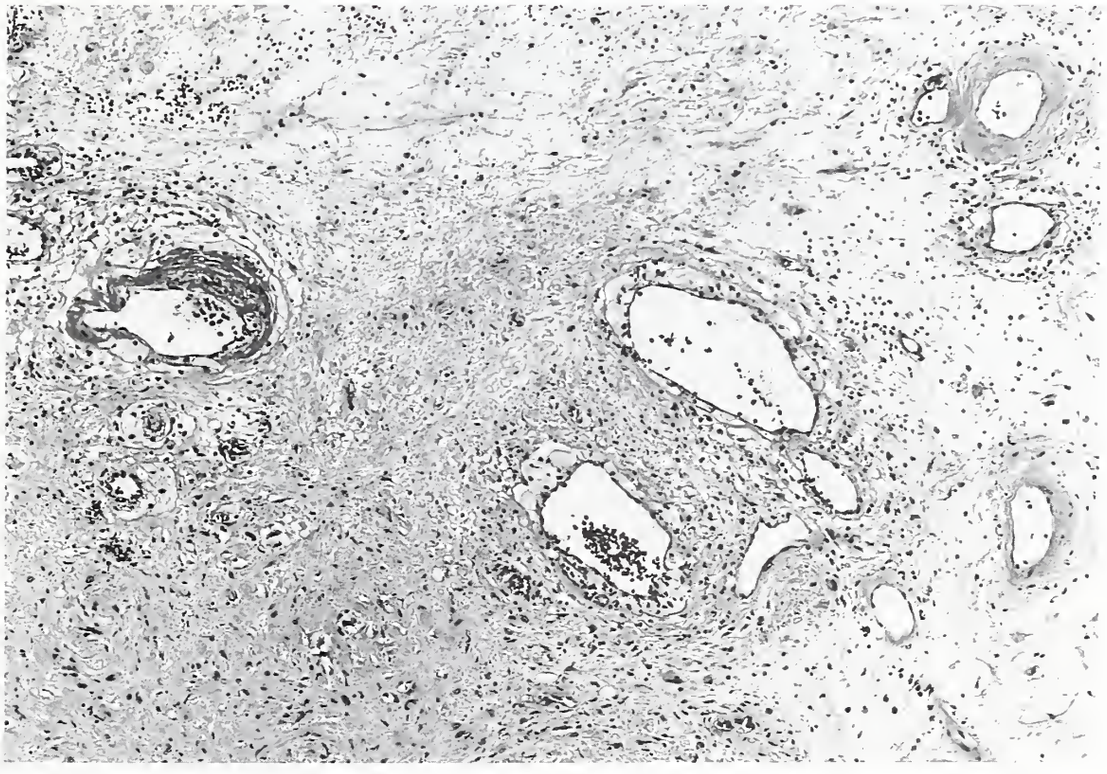


Figure 4-11
SCHWANNOMA
An area of degeneration reveals edematous tissue with dilated blood vessels, whose walls show hyalinization or fibrin deposition. Viable tumor tissue is evident in a small area.

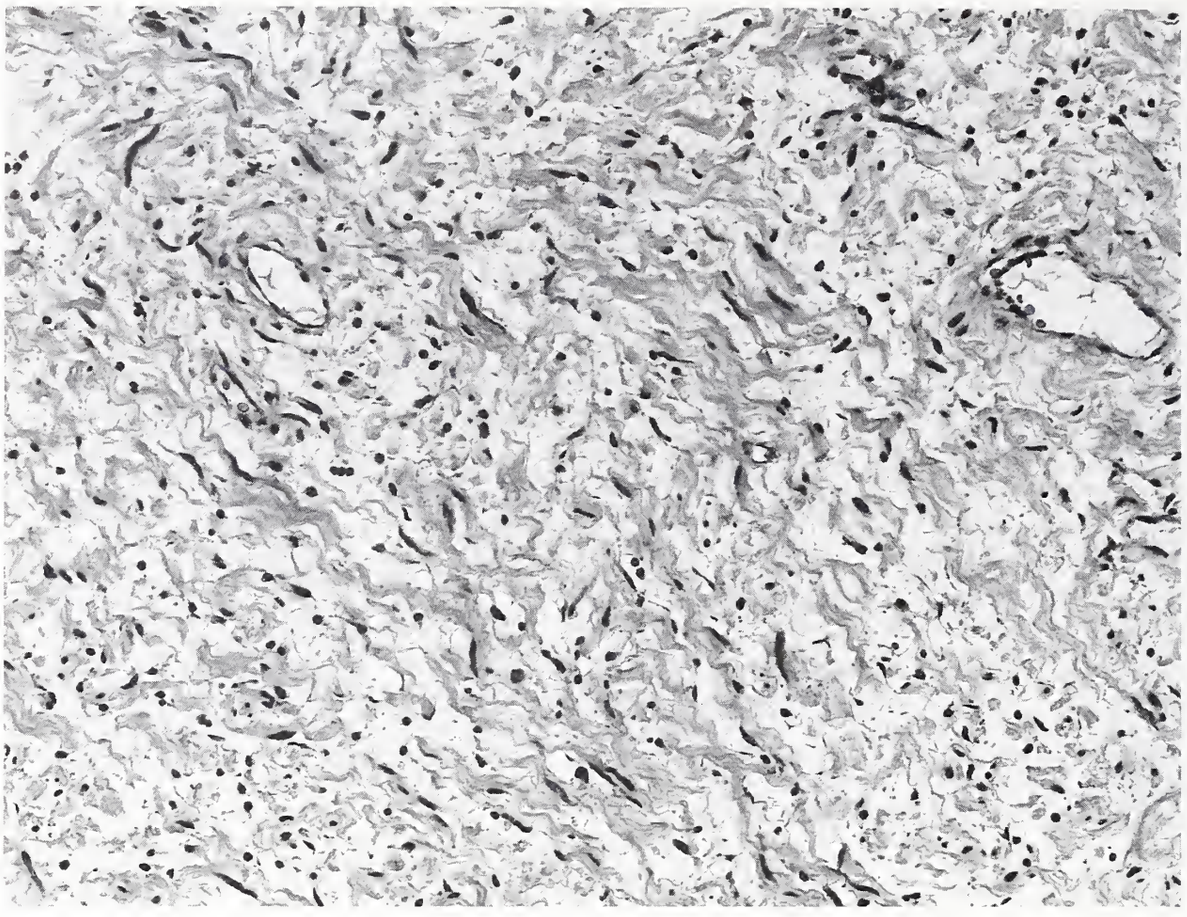


Figure 4-12
NEUROFIBROMA
Wavy elongated cells are present in an edematous matrix with some collagenization.

not encapsulated or cystic. In many cases neurofibroma can be diagnosed easily by its characteristic features (fig. 4-12), but it may be difficult to differentiate neurofibroma and schwannoma because of mixed histologic patterns. This probably results from the constituent cells of the former: fibroblasts, Schwann cells, and neurites. Solitary neurofibroma rarely shows malignant transformation and surgical resection leads to cure. It occasionally occurs in neurofibromatosis.

Neurofibromatosis is an autosomal dominant congenital disease in which the abnormality is in chromosome 17q11.2 (NF1 tumor suppressor gene) (15,21). In the mediastinum, the vagus nerve and sympathetic chains are often involved, frequently showing plexiform neurofibromas. Neurofibromatosis involving the mediastinum is categorized as peripheral neurofibromatosis (neurofibromatosis type 1) and is often associated with cafe-au-lait spots. It may be complicated by a variety of tumors such as schwannoma, ganglioneuroma, pheochromocytoma, medullary carcinoma of the thyroid, and nephroblastoma, but very rarely with central nervous system tumors.

Spindle cell malignant tumor of the nerve is variously designated as neurofibrosarcoma, neurogenic sarcoma, malignant schwannoma, and malignant tumor of nerve sheath origin, but *malignant peripheral nerve sheath tumor* is the preferred designation. It is rare in the mediastinum, and is more frequent in the posterior mediastinum than in the other compartments. It is often large and causes symptoms when detected, compressing, displacing, or invading the intrathoracic organs and thoracic wall. The prognosis is less favorable in cases complicated with neurofibromatosis than in cases with a solitary lesion.

Tumors of sympathetic ganglia in the posterior mediastinum include benign ganglioneuroma and malignant ganglioneuroblastoma and neuroblastoma. *Ganglioneuroma* occurs in the retroperitoneum and posterior mediastinum.

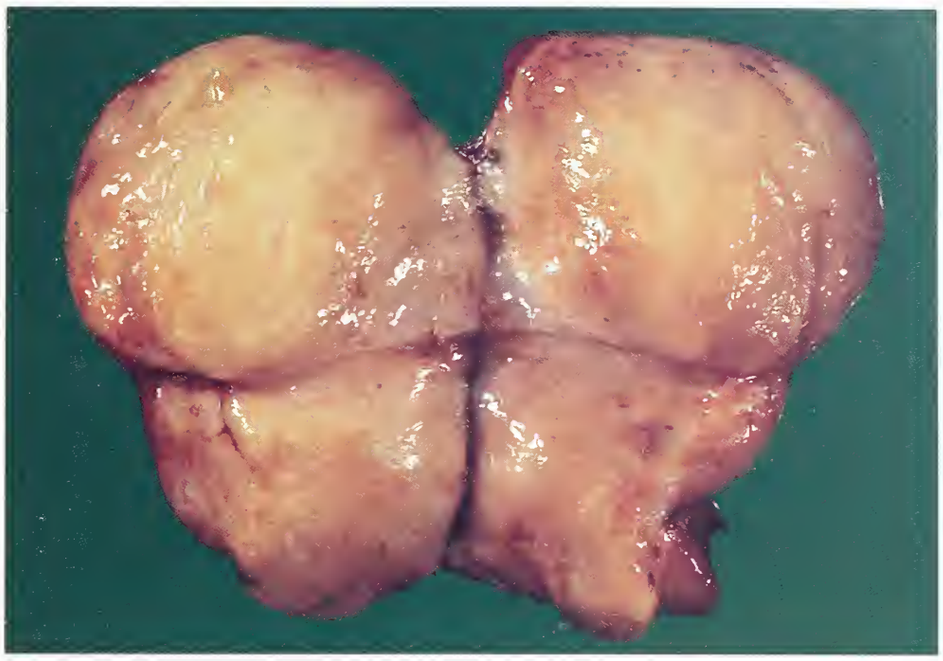


Figure 4-13
GANGLIONEUROMA
Tumor is encapsulated and its cut surface bulges. It is pale tan and faintly trabeculated.

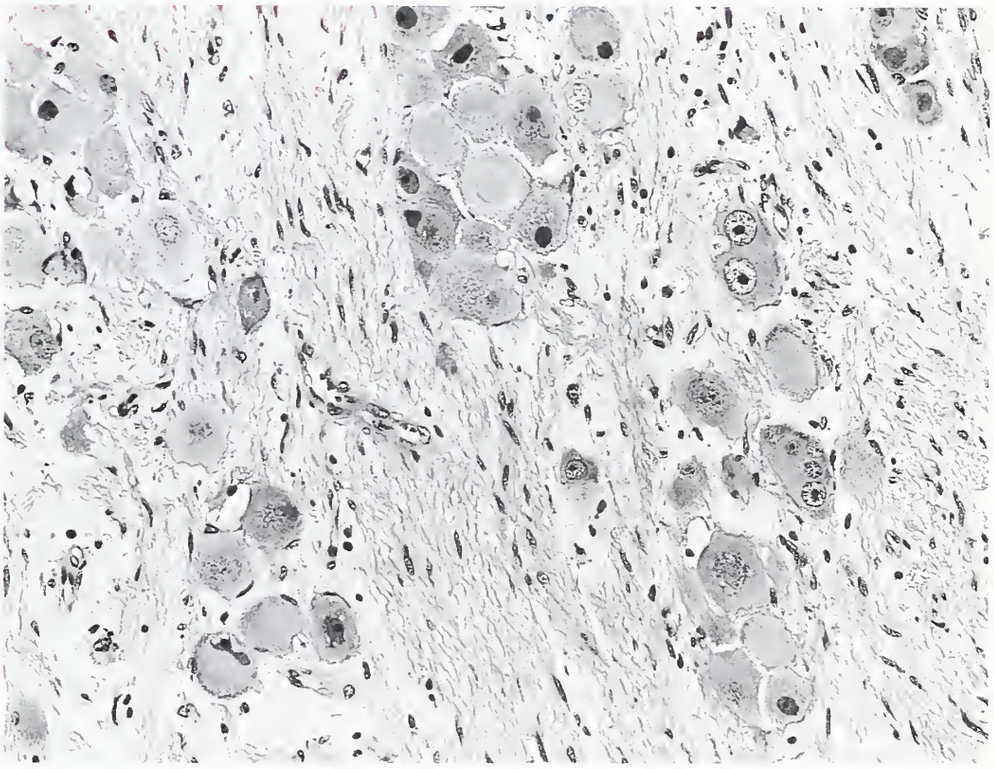


Figure 4-14
GANGLIONEUROMA
The tumor consists of mature ganglion cells, nerve fibers, and Schwann cells.

It arises de novo, but may result from maturation of neuroblastoma, and is seen in children and young adults. It is often large and encapsulated. The cut surface bulges, and is pale tan and faintly trabeculated (fig. 4-13). It is composed of mature ganglion cells with Nissl granules, Schwann cells, and nerve fibers (fig. 4-14). Granular calcified materials may be scattered.

Neuroblastoma is the most common malignant tumor of early childhood, most frequently occurring in the adrenal medulla. It also occurs in the extra-adrenal sympathetic ganglia of the retroperitoneum and posterior mediastinum, although much less frequently. There were only 2 cases among 67 surgically resected mediastinal neurogenic tumors at the National Cancer Center

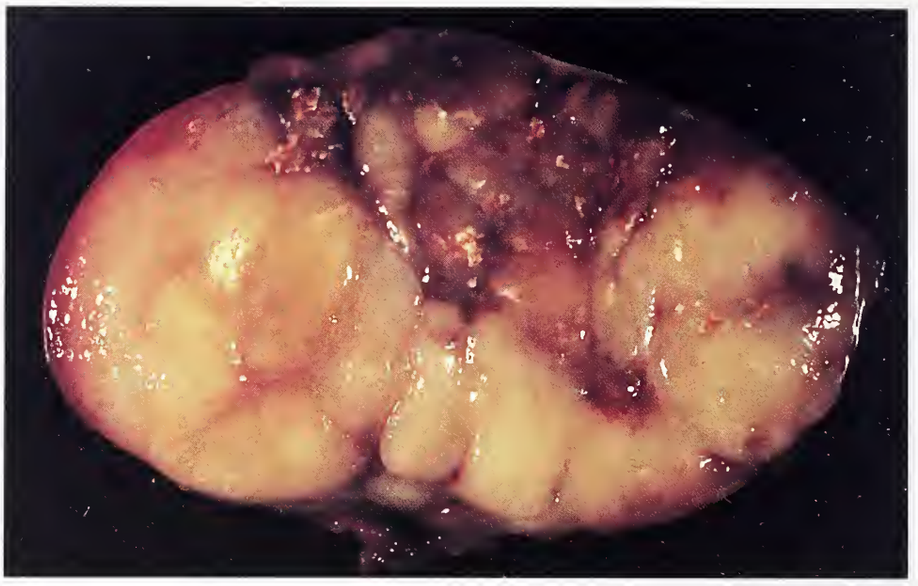


Figure 4-15
NEUROBLASTOMA
The tumor is encapsulated and soft. The cut surface bulges, and is nodular or lobulated with areas of hemorrhage.

Hospital in Tokyo (see Table 3-3). Neuroblastoma may be congenital: about half of the patients are under the age of 2 years, and most tumors are detected before 5 years of age. It is associated with loss of heterozygosity for chromosome 1p which probably occurs at early stages of tumor development and amplification of oncogene N-*myc* at an advanced stage (18,28–30).

Patients with mediastinal neuroblastoma often present with symptoms due to compression by tumor of neighboring structures and Horner's syndrome as a result of sympathetic nerve damage. Elevated plasma and urinary levels of catecholamines and elevated urinary level of vanillylmandelic acid (VMA) have diagnostic value. The latter is used for screening newborns and infants for this tumor.

The tumor is often large, encapsulated, and soft, with areas of hemorrhage on cut sections (fig. 4-15). Histologically, it can be divided into well- and poorly differentiated neuroblastomas. In the well-differentiated form, in addition to small "neuroblasts," frequent Homer-Wright type rosettes and neurofibrillary material are evident (fig. 4-16). Large and multinucleated cells may be present but differentiation toward ganglion cells is not evident. In poorly differentiated neuroblastoma, rosettes and neurofibrillary material are rare or absent.

Tumors consisting of neuroblasts, ganglion cells, and intermediate cells in various proportions are called *ganglioneuroblastomas*. They are also divided into well- and poorly differentiated forms depending upon the amount of neuroblasts and degree of maturation toward ganglion cells (fig. 4-17). Furthermore, there is a composite type ganglioneuroblastoma, which is composed partially of ganglioneuroma or ganglioneuroblastoma and partially of neuroblastoma. A case of ganglioneuroblastoma arising in the thymus of a 61-year-old woman with the syndrome of inappropriate secretion of antidiuretic hormone has been reported recently, which is most unusual in terms of the location, age of the patient, and paraneoplastic syndrome (14a).

The prognosis of patients with neuroblastoma is poor, in spite of aggressive treatment, and the overall 2-year survival rate is said to be 60 percent (17). However, survival rates depend on a number of factors including the age of the child at the time of diagnosis, stage of the disease, location and degree of histologic differentiation of the tumor, and presence of neuron-specific enolase (NSE), ferritin, DNA ploidy, and amplification of the N-*myc* gene (16,17,30). Age and stage are two independent variables and are also the two most important prognostic factors. Favorable prognostic factors in neuroblastoma are: a young age (less than 2 years), a favorable histologic type, no N-*myc* amplification, low serum ferritin, hyperdiploidy, and high expression of the *TRK* gene (16). The better prognosis of patients with mediastinal neuroblastoma compared to those with retroperitoneal or adrenal tumors is probably due to an earlier tumor stage at detection. Although rare, spontaneous regression of neuroblastoma

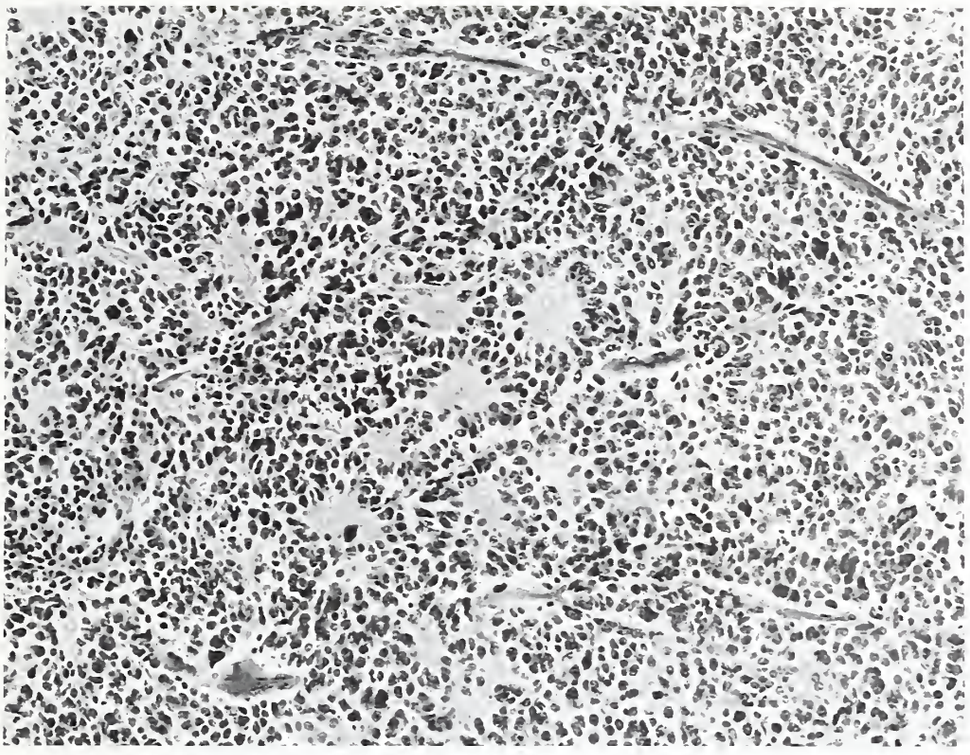


Figure 4-16
NEUROBLASTOMA
The tumor consists of diffuse growth of small hyperchromatic cells ("neuroblasts") and frequent rosettes of Homer-Wright type.

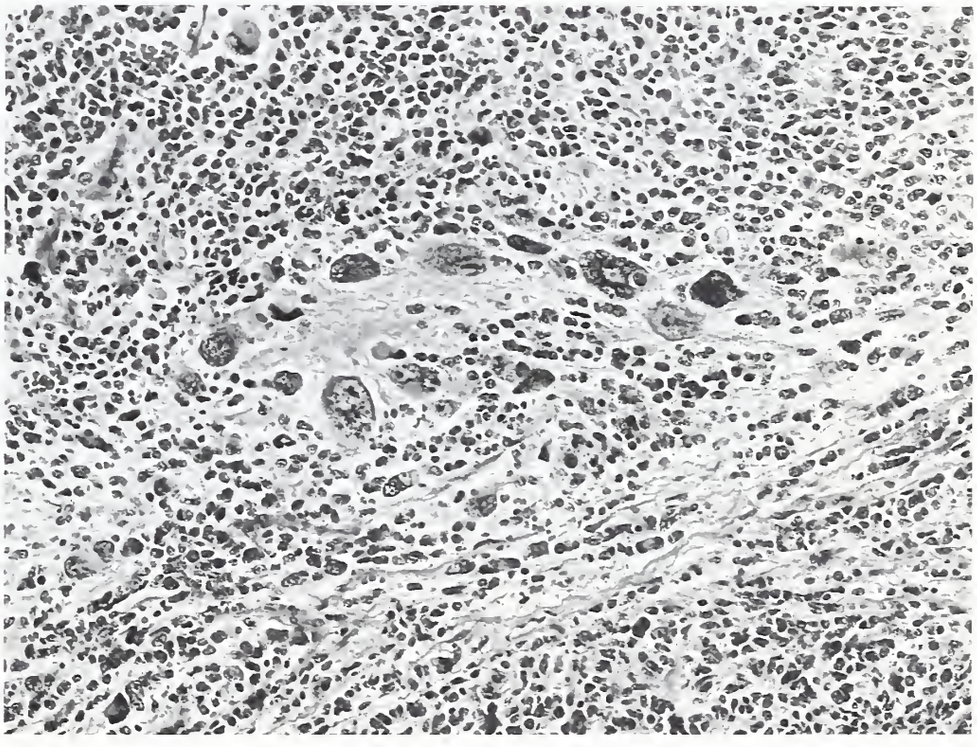


Figure 4-17
GANGLIONEUROBLASTOMA
The tumor consists of diffuse growth of small hyperchromatic cells, in which a cluster of immature ganglion cells with neurofibrillary material is present. This is a poorly differentiated form of ganglioneuroblastoma.

has been reported, showing maturation into ganglioneuroma. The prognosis of ganglioneuroblastoma is much better than that of less differentiated neuroblastoma: the 5-year actuarial survival rate is 88 percent (14).

The *primitive neuroectodermal tumor (PNET)* is rare in the mediastinum. Wick (31) saw two cases: one in the anterior mediastinum and one in the posterior mediastinum in an adolescent and a young adult. PNET must be differentiated from poorly differentiated neuroblastoma.

An extremely rare *mediastinal ependymoma* was found in the paravertebral region, and it was recognized not to be in continuity with the spinal

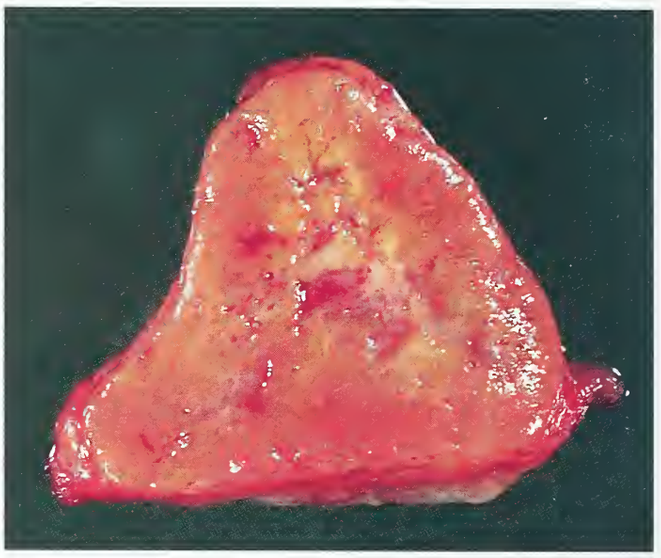
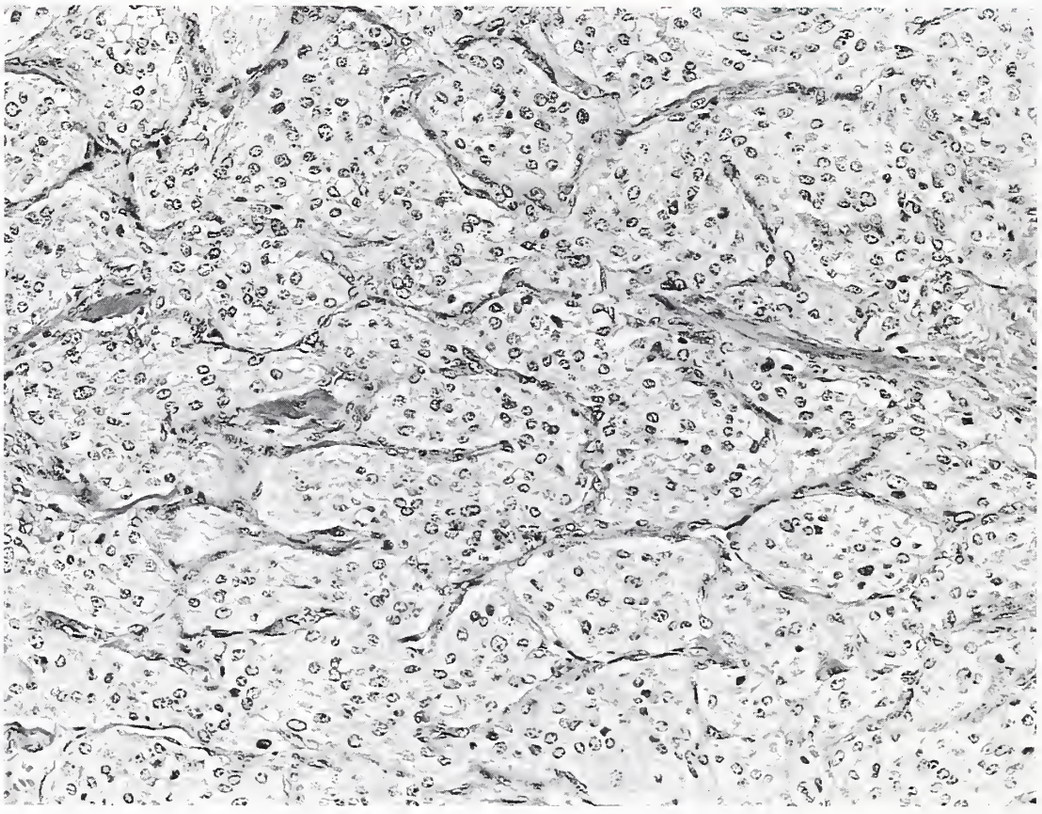


Figure 4-18
PARAGANGLIOMA

Right: The cut surface of a 3.9 x 3.5 x 2.5 cm tumor is triangular, with a bulging peripheral portion and a somewhat fibrotic center. It was surrounded by the heart, left lower lobe of the lung, aorta, esophagus, and diaphragm, and had been 1.8 cm in diameter 7 years before.

Below: The tumor is composed of "zellballen" bordered by capillaries. Individual cells were Grimelius positive.



canal. Histologically, there was palisading of elongated tumor cells around fibrovascular cores and ciliated cells in gland-like structures. The diagnosis was confirmed by positive immunohistochemical staining for glial fibrillary acidic protein and by electron microscopic detection of cilia within intracytoplasmic vacuoles (26).

Pigmented neuroectodermal tumor of infancy, (melanotic progonoma or *retinal anlage tumor),* which involves the jaws of infants, also occurs in the mediastinum (23). It was originally thought to be benign, but is now considered malignant because of recurrence and metastasis in some cases (27).

Paragangliomas originate from aorticopulmonary paraganglia present in the superior and middle mediastinum and from aorticosympathetic paraganglia in the posterior mediastinum. Histologically, they are characterized by zellballen of polygonal tumor cells bordered by capillaries (fig. 4-18). Moran et al. (24) reviewed 16 cases of mediastinal paragangliomas collected from the files of

the Armed Forces Institute of Pathology. Features included stromal hyalinization, a prominent spindle cell component, and granular cell changes in the cytoplasm of tumor cells in some cases. The reviewers concluded that the only parameter that correlated with aggressive behavior was the extent of circumscription or local infiltration of the tumor at initial resection, and recommended regular follow-up of patients due to the potential of the tumor to metastasize.

Immunohistochemistry of Neurogenic Tumors and Paragangliomas

Neuron-specific enolase (NSE) can be demonstrated in neurogenic tumors. If fresh frozen or cold acetone-fixed tissues are available, neural cell adhesion molecule (N-CAM) immunostains in almost all neurogenic and neuroendocrine tumors (19). In addition, schwannoma and neuroblastoma can be differentiated by their staining for S-100 protein and synaptophysin, respectively (25). Catecholamines can be detected by formalin-induced fluorescence. According to Wirnsberger et al. (32), NSE, chromogranins and related proteins (HISL 19), dopamine beta-hydroxylase, protein gene product (PGP) 9.5, neurofilaments, and endocrine granule constituents (EGC) are excellent markers for neuroblastic tumors since they are present in most cases; S-100 protein is present in ganglioneuroblastomas and ganglioneuromas.

Moran et al. (24) found immunoreactive chromogranin A and S-100 protein in most paragangliomas and leu-enkephalin and neurofilament protein in about half. To distinguish paragangliomas from carcinoid tumors, both of which are Grimelius positive, stain for chromoganin A immunohistochemically, and in some cases for S-100 protein, cytokeratin is used, since it is negative in the former and positive in the latter. Other immunopositive substances in carcinoid tumors include a variety of amine and peptide hormones.

MEDIASTINAL CYSTS (OTHER THAN THYMIC CYST)

The various cysts in the mediastinum can be divided into two main categories: congenital and acquired (Table 4-2). Thymic cysts, both congenital and acquired, have been described separately.

Table 4-2

MEDIASTINAL CYSTS AND CYST-LIKE LESIONS

- Cysts
  - Congenital
    - Bronchogenic
    - Esophageal
    - Tracheoesophageal
    - Gastroenteric
    - Celomic (pericardial, mesothelial)
    - Thymic
  - Acquired
    - Thoracic duct
    - Lymphangioma
- Cyst-like lesions
  - Hematoma
  - Parasitic
  - Cystic changes in:
    - Thymic hyperplasia
    - Thymoma
    - Thymic carcinoma
    - Mature teratoma (dermoid cyst)
    - Germinoma
    - Low-grade B-cell lymphoma of MALT
    - Hodgkin's disease

Mediastinal cysts are uncommon lesions, comprising 10 to 27 percent of all mediastinal space-occupying lesions according to Marchevsky and Kaneko (34). Of the surgically resected mediastinal lesions in the last 30 years at our institute, only 39 (12 percent) were cysts (see Table 3-3).

The majority of patients with mediastinal cysts and cystic lesions have no symptoms and the cysts are found incidentally on chest X-ray examinations performed routinely or for other purposes. However, solid and cystic lesions cannot be differentiated by plain chest roentgenograms, and CTs, without and with contrast medium, help distinguish cystic from solid lesions in many but not all cases. Echography is also helpful in the differential diagnosis. However, the most effective approach for diagnosing cystic lesions is percutaneous or transbronchial needle aspiration of the contents and cytologic examination of the aspirated fluid. With this method, together with the location of the lesions, not only the type of lesion, either

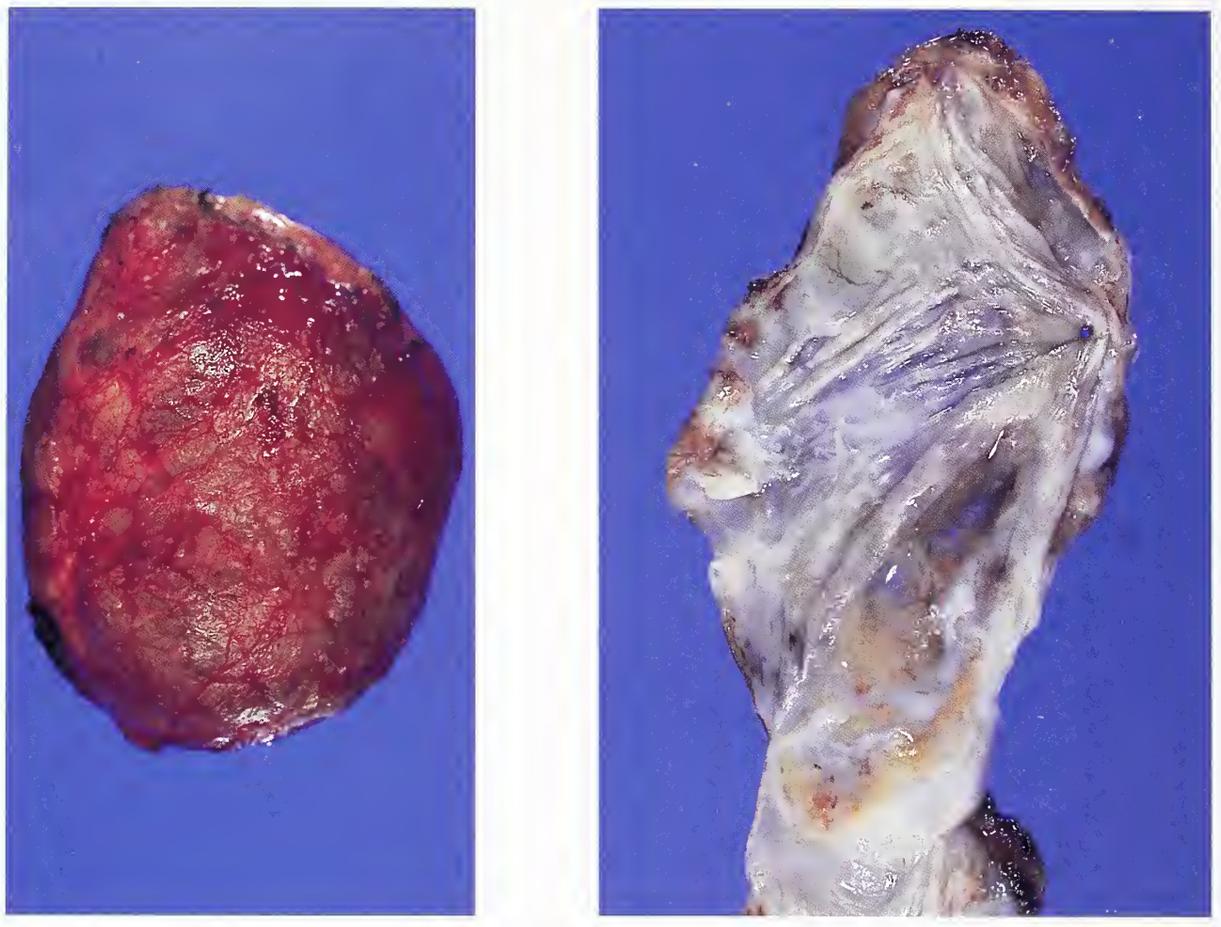


Figure 4-19
BRONCHOGENIC CYST
Left: A thin-walled cyst which was present in the posterior mediastinum is distended with slightly cloudy somewhat mucinous fluid. Right: The inner surface is smooth and trabeculated in areas.

cystic or solid, but also the nature of the lesion, can be determined or at least suspected in most cases. For example, straw colored clear fluid is obtained from celomic cysts and some congenital thymic cysts, mucinous cloudy fluid from bronchogenic cysts, chylous fluid from thoracic duct cysts, and muddy or grumous material from mature cystic teratomas. Cytologic examination establishes the nature of cystic lesions as either benign or malignant and often determines the cell type or cell of origin as either mesothelial, squamous, or respiratory epithelial cell type.

Bronchogenic Cyst

Bronchogenic cyst is the most common congenital cyst of the mediastinum. While it can be found at any age, it is more frequently found in young adults. It results from abnormal branching of the tracheobronchial tree during embryonic development. Patients are asymptomatic in many cases but the cyst may produce symptoms due to compression of the surrounding structures such as the trachea, bronchi, and esophagus by an enlarged cyst.

Bronchogenic cysts are frequently located in the anterior mediastinum and often connected by fibrous tissue with the trachea or bronchi, but may be present in other parts of the mediastinum and within the lung parenchyma. The cysts are spherical, usually unilocular but may be multiloculated, and thin-walled with a smooth outer surface and faintly trabeculated inner lining (fig. 4-19).

The cyst is lined with respiratory epithelium (fig. 4-20), that is, pseudostratified ciliated columnar epithelium, which may show squamous metaplasia or be denuded. Tracheobronchial glands are present in the lamina propria, at times even outside the smooth muscle layer of the wall. Cartilage may also be present.

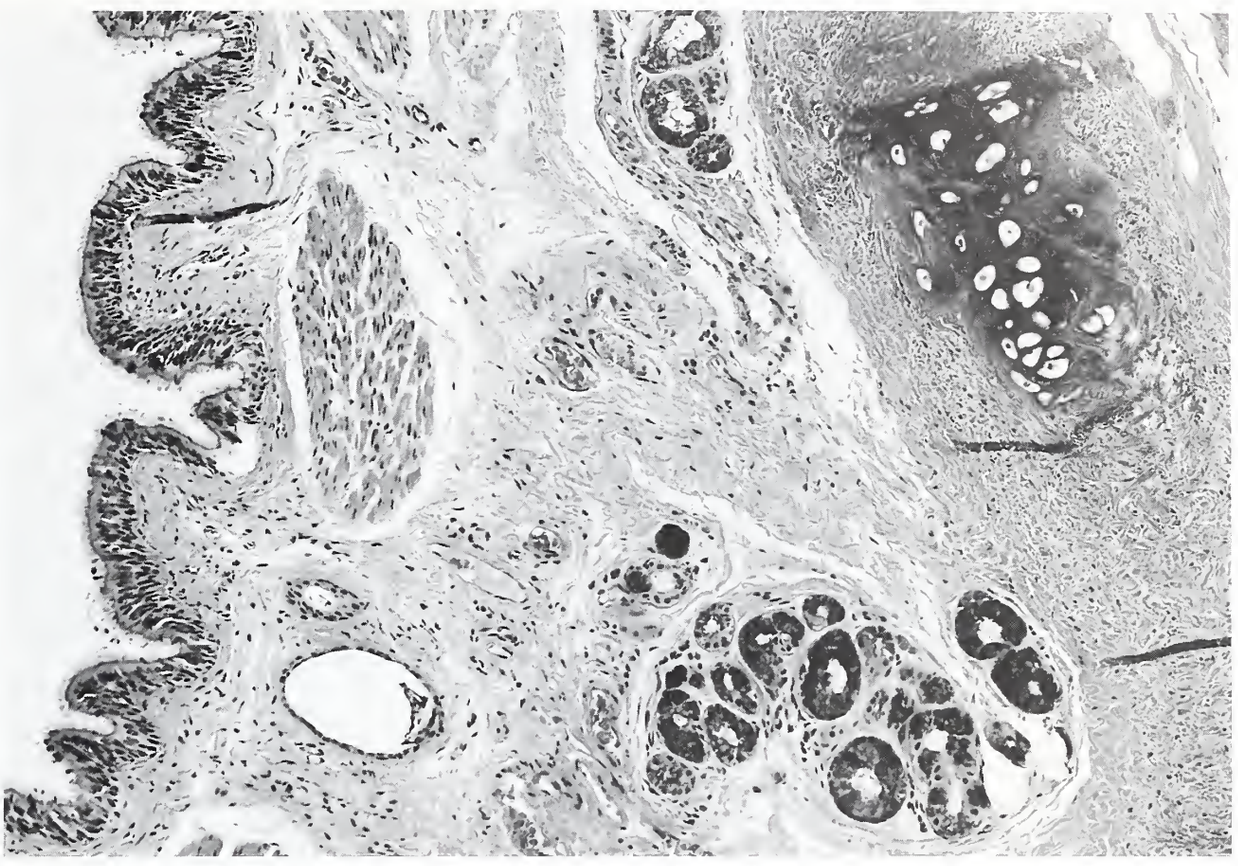


Figure 4-20
BRONCHOGENIC CYST
The cyst is lined by pseudostratified ciliated columnar epithelial cells and the wall contains accessory glands, layers of smooth muscle, and cartilage.

Surgical removal is the treatment of choice for cysts causing symptoms. Percutaneous needle aspiration of the contents is also indicated for symptomatic relief. In such cases the content should be examined cytologically.

Esophageal Cyst

Esophageal cysts are much less common than bronchogenic cysts, and present within the wall of, or in close association with, the esophagus. They are spherical and unilocular, and lined by stratified squamous epithelium with or without foci of ciliated columnar epithelium. The epithelium is supported by the lamina propria with esophageal glands and surrounded by a double layer of smooth muscle, the lamina muscularis propria. These cysts are differentiated from bronchogenic cysts by location, absence of cartilage, and the presence of muscularis propria. However, the nature of the cyst cannot be determined at times because of the absence of characteristic features.

Tracheoesophageal cysts are rare and have the combined features of bronchogenic and esophageal cysts.

Gastroenteric Cyst

Gastroenteric cysts are rare developmental unilocular cysts found in the posterior mediastinum, frequently connected to the vertebral column with fibrous tissue. They are found often in infants as well as adults. Gastroenteric cysts are reported to be frequently associated with malformations of the cervical and thoracic vertebrae such as hemivertebrae, posterior spina bifida, and scoliosis (34,36). Patients are symptomatic when diagnosed and present with pain due to compression of nerves, peptic ulceration of the lining mucosa and wall, and other symptoms due to involvement of surrounding mediastinal structures.

The cyst is lined by either gastric mucosa with parietal and chief cells; duodenal, small intestinal, and large intestinal mucosae; or squamous

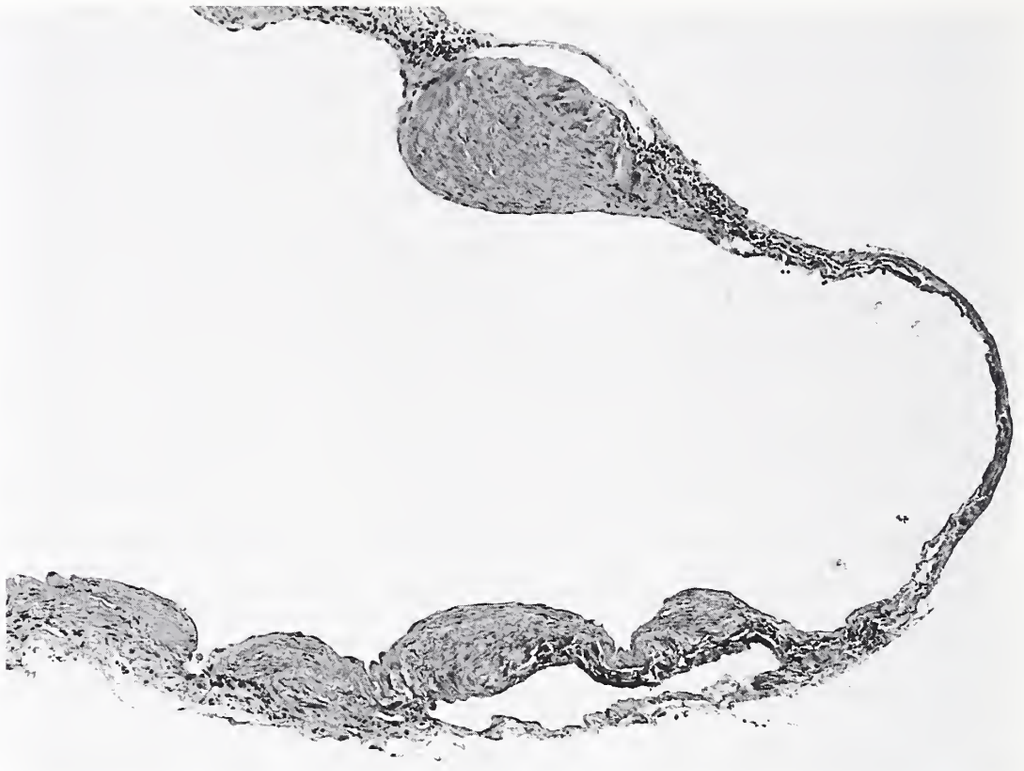


Figure 4-21
PERICARDIAL CYST
A thin-walled cyst is lined by a single layer of flat cells. Focal fibrous thickening is seen in a thin fibrous wall.

or ciliated columnar epithelium. Outside the lamina propria mucosae, there is lamina muscularis mucosae, submucosa, and lamina muscularis propria.

Peptic digestion of the wall produces sinuses and fistulae into the chest wall and thoracic organs and can be fatal. Development of adenocarcinoma of the colonic type in gastroenteric cyst has been reported (34).

Celomic Cyst (Pericardial Cyst and Mesothelial Cyst)

Celomic cysts are occasionally seen in the mediastinum, either attached to the pericardium (pericardial cyst) or in other parts of the mediastinum (mesothelial cyst). Patients are often asymptomatic, and the cysts are detected incidentally at the time of chest X-ray examination, or there are symptoms due to compression of the mediastinal structures by the cyst. Cysts are spherical, unilocular, and thin walled. The content is watery clear or straw colored. They are lined by a single layer of flat to cuboidal mesothelial cells supported by loose connective tissue (fig. 4-21) and can be treated surgically or by percutaneous aspiration of the cyst content.

Thoracic Duct Cyst

Thoracic duct cysts are rare, although subdiaphragmatic cisterna chyli cysts are not uncommon. Tsuchiya et al. (37) reported a case of thoracic duct cyst diagnosed before thoracotomy. The patient was a 49-year-old woman who began to experience eructation. The left lateral chest roentgenogram revealed an ovoid density behind the hilus of the lung. The lesion was cystic and enclosed by, but not connected with, bronchi, esophagus, vertebrae, and descending aorta as assessed by CT, barium swallow, and aortography. Therefore, the cyst was considered to be associated with the thoracic duct, and it was proved to be so by lymphangiography taken 24 hours after injection of iodized oil into the lymphatic vessel of the patient's foot. It was a thin-walled unilocular cyst containing chylous fluid and clotted substance. The internal surface was trabeculated and lined by flat endothelial cells.

Cyst-like Lesions Other Than True Cysts

Hematoma is often the result of trauma, but may be spontaneous. Hydatidic cyst, described in the second series of this Fascicle, is found in

Figure 4-22
CASTLEMAN'S DISEASE
A chest roentgenogram reveals that a mass is located to one side of the midline, which frequently occurs. In this case, a well-defined tumorous lesion projects toward the left thoracic cavity.

endemic areas (35). On rare occasions, germinoma and Hodgkin's disease of the thymus may undergo extensive cystic change to the point of obscuring the true nature of the process (35). Cystic changes in thymoma and thymic carcinoma were described in previous chapters. Low-grade B-cell lymphoma of mucosa-associated lymphoid tissue is also cystic (see fig. 3-211) (33).

OTHER MEDIASTINAL TUMOR-LIKE CONDITIONS

Castleman's Disease

Castleman's disease, also commonly referred to as *angiofollicular* or *giant lymph node hyperplasia,* was initially described as a solitary lesion in the mediastinum, which is the most common site of involvement (44). It has now been reported in many other locations including the abdominal cavity, pulmonary parenchyma, neck, axillary regions, and skeletal muscle. Castleman's disease involving the mediastinum consists of a well-circumscribed round nodule (usually in the anterosuperior portion), with a tendency to be on one side of the midline at a lung root, around one of the great vessels, or close to an interlobar fissure (fig. 4-22).

Two forms of Castleman's disease have been identified: the much more common localized type and the less common multicentric type (38,44). Although the latter has histologic features similar to the former, the multicentric type develops in older patients, is consistently a peripheral rather than central nodal disease, and has a more aggressive clinical course often associated with the development of malignancies. It is beyond

the scope of this chapter to discuss the details of the multicentric type, and description is restricted to the localized type.

Involvement of the thymus by Castleman's disease, either in the multicentric or solitary form, is extremely rare. Multicentric Castleman's disease with prominent thymic involvement was reported by O'Reilly et al. (41) in a 12-year-old girl and a localized form of giant lymph node hyperplasia involving the thymus was reported by Karcher et al. (39). The latter was associated with nephrotic syndrome and myelofibrosis, and thymic involvement was thought to be secondary due to the proximity of the primary nodal site of Castleman's disease.

The localized or solitary lesions of Castleman's disease are usually rounded masses varying from 1.5 to 16 cm in diameter. Histologically, two major types have been described: hyaline-vascular type and plasma cell type (38,42–44); intermediate and mixed types have also been reported. The hyaline-vascular type is much more common than the plasma cell type, comprising 90 percent of the cases in a large series (40). The two types differ considerably in their histologic appearance and clinical presentation. Patients with the hyaline-vascular type are mostly asymptomatic, unless the mass causes pressure symptoms by compressing adjacent structures such as the trachea or bronchi. Patients with the plasma cell type often present with systemic symptoms and abnormal laboratory data (44). Following total excision of the mass, the symptoms disappear and laboratory data return to normal.

Hyaline-Vascular Type. This type may occur in children as well as adults (median age, 33 years in one series [44]). This is also true for the plasma cell type (median age, 22 years). There is no predilection for either sex. Macroscopically, the lesion consists of a single encapsulated mass. The cut surface is solid, homogeneous, gray, finely granular or nodular, and sometimes hemorrhagic (fig. 4-23). The main histologic features include abnormal follicles and a striking interfollicular vascularity. The latter feature accounts for the significant bleeding if the lesion is incised during surgery. The follicles often have expanded mantle zones composed of small lymphocytes surrounding abnormal germinal centers, which range in size from medium to barely recognizable (fig. 4-24). Most

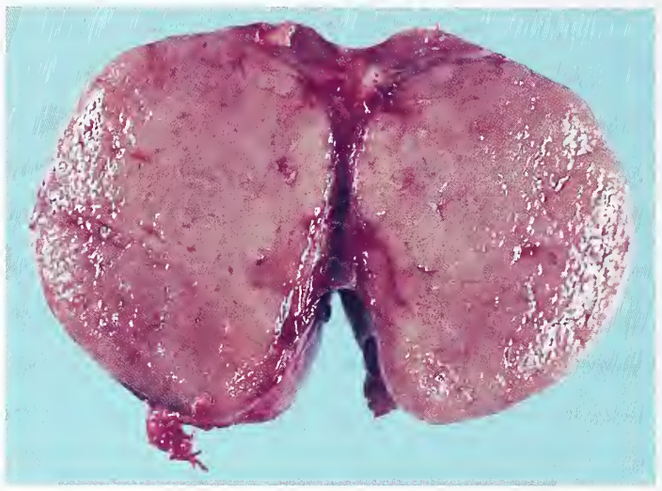


Figure 4-23
MACROSCOPIC APPEARANCE
OF CASTLEMAN'S DISEASE
Cut surface is granular to nodular.

of the germinal centers are small, while larger ones are also present and abnormal. The follicles contain one or more small blood vessels entering from the perifollicular tissue (fig. 4-25). Some of these vessels have hyalinized and thickened walls in the center of the germinal centers, which superficially resemble Hassall corpuscles or splenic white pulp (44); the former can be mistaken for thymoma, and the latter for ectopic spleen. Some of the germinal centers may be surrounded by greatly expanded, concentrically arranged ("onion skin"), small mantle zone lymphocytes which may completely obscure the germinal centers (fig. 4-26). When these histologic features predominate, the lesion is referred as the lymphoid variant of the hyaline-vascular type. Another characteristic finding is the presence of more than one small germinal center within a single follicle (fig. 4-27). The interfollicular areas contain varying numbers of small blood vessels, which may be extremely numerous. Most are lined by flat endothelium, but some have prominent endothelial cells and resemble postcapillary venules. Small lymphocytes are the predominant cells between vessels; a small number of plasma cells and rare immunoblasts may be present as well. Large fibrotic masses, which often surround larger vessels, are often scattered in the interfollicular zones. Lymph node architecture, such as sinuses, is often seen at the periphery of the lesion.

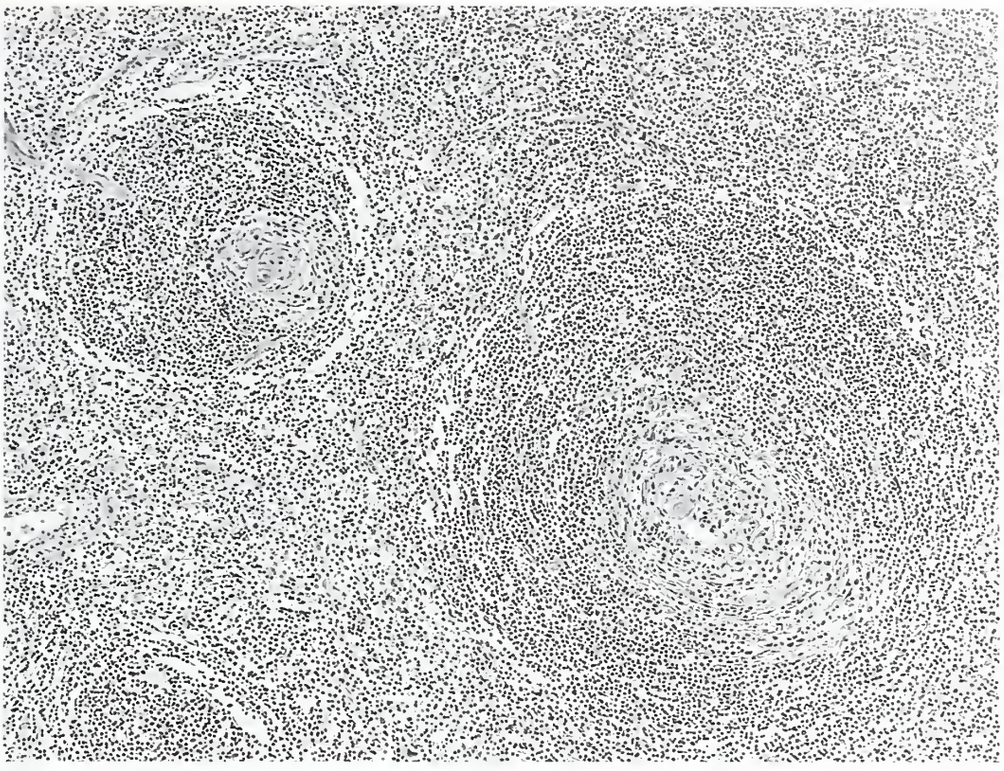


Figure 4-24
CASTLEMAN'S DISEASE, HYALINE-VASCULAR TYPE
The follicles consist of atrophic germinal centers surrounded by a wide mantle zone of concentrically arranged lymphocytes. The interfollicular areas are highly vascular with a network of small vessels.

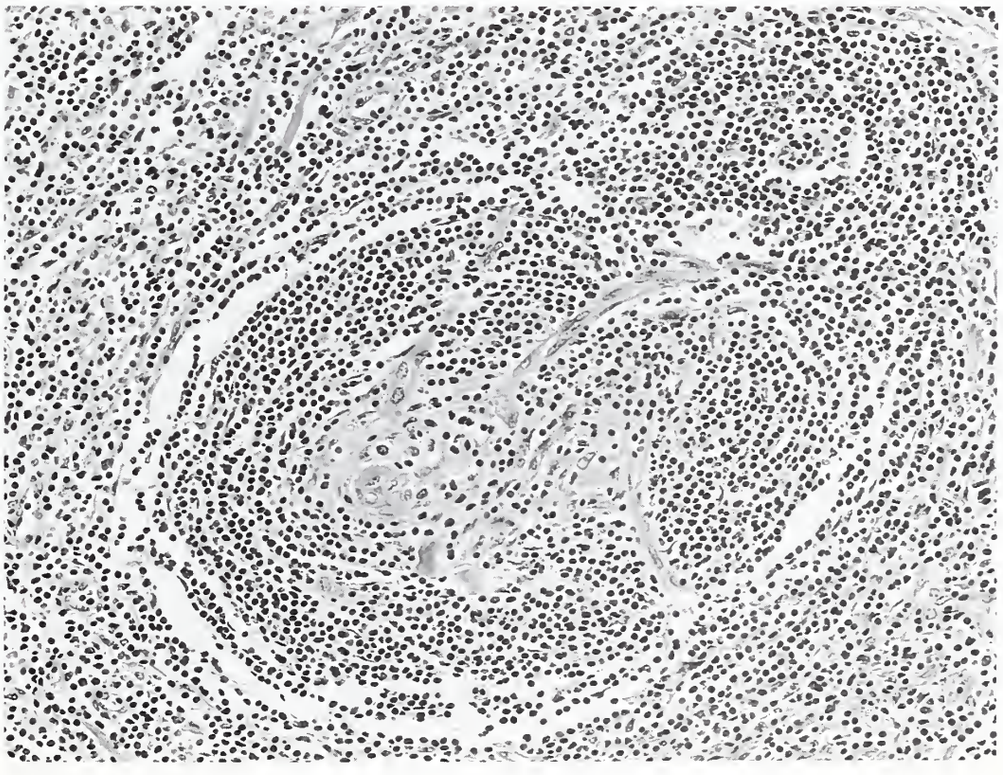


Figure 4-25
CASTLEMAN'S DISEASE, HYALINE-VASCULAR TYPE
An atrophic germinal center contains a few small blood vessels entering from perifollicular tissue.

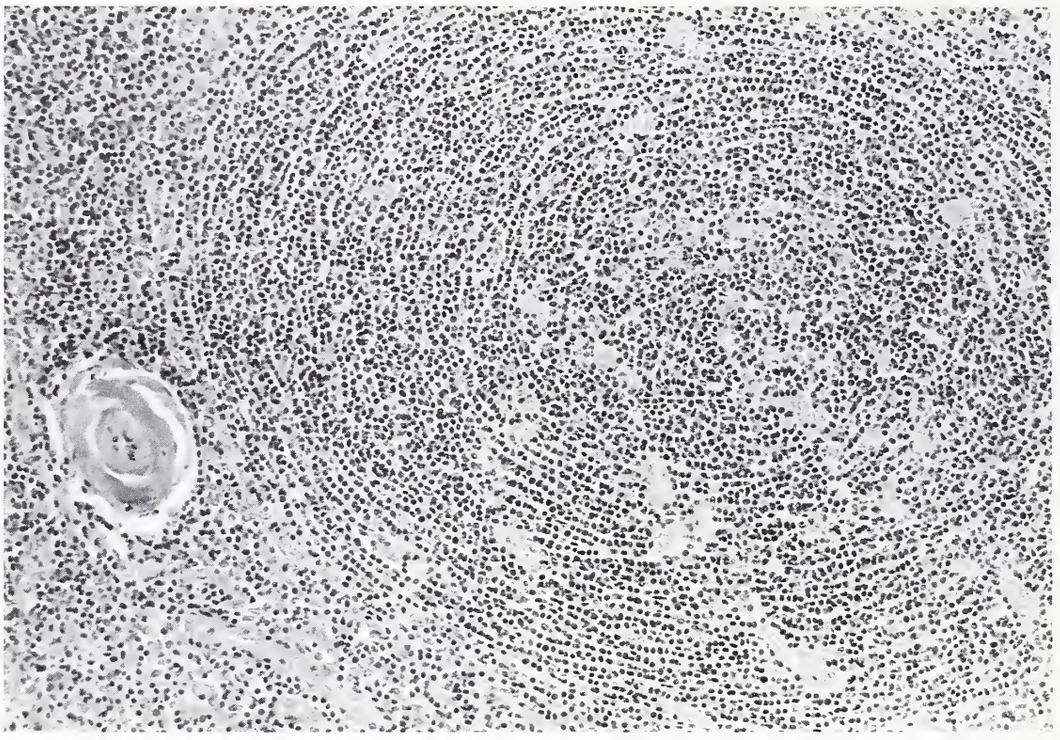


Figure 4-26
CASTLEMAN'S DISEASE, LYMPHOID VARIANT

The follicle is composed entirely of concentrically arranged small lymphocytes. Perivascular fibrosis is present in the interfollicular area. (Fig. 281 from Schnitzer B. Reactive lymphadenopathies. In: Knowles DM, ed. Neoplastic hematopathology. Baltimore: Williams & Wilkins, 1992:427–57.)

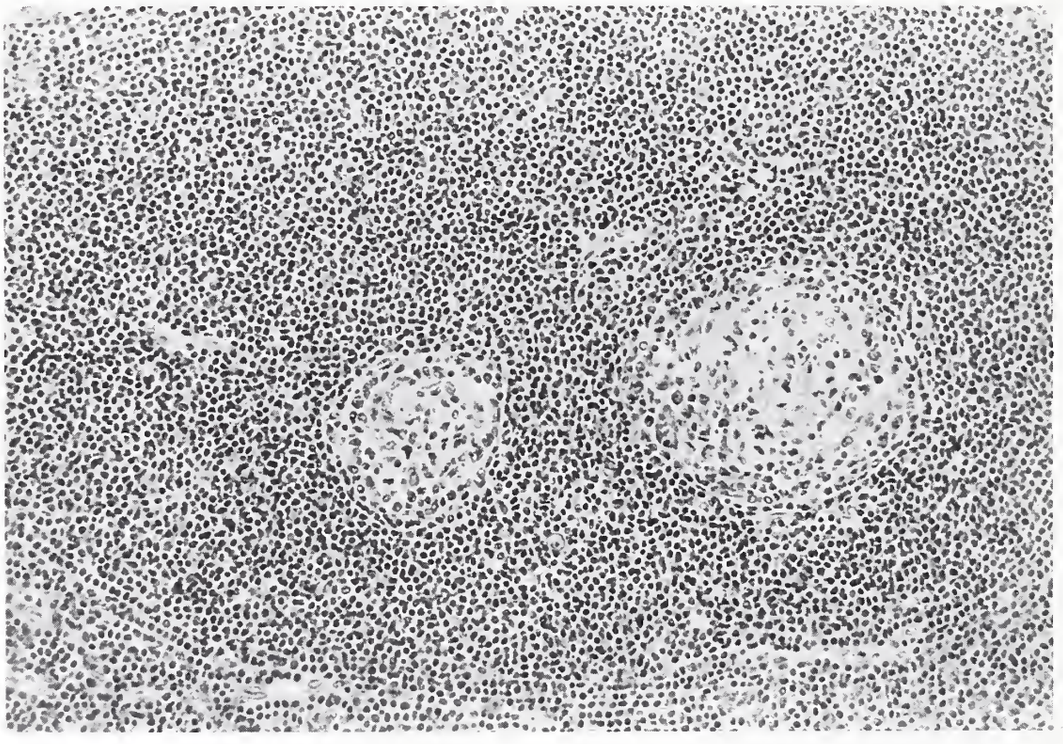


Figure 4-27
CASTLEMAN'S DISEASE, HYALINE-VASCULAR TYPE

A single follicle contains two atrophic germinal centers. (Fig. 282 from Schnitzer B. Reactive lymphadenopathies. In: Knowles DM, ed. Neoplastic hematopathology. Baltimore: Williams & Wilkins, 1992:427–57.)

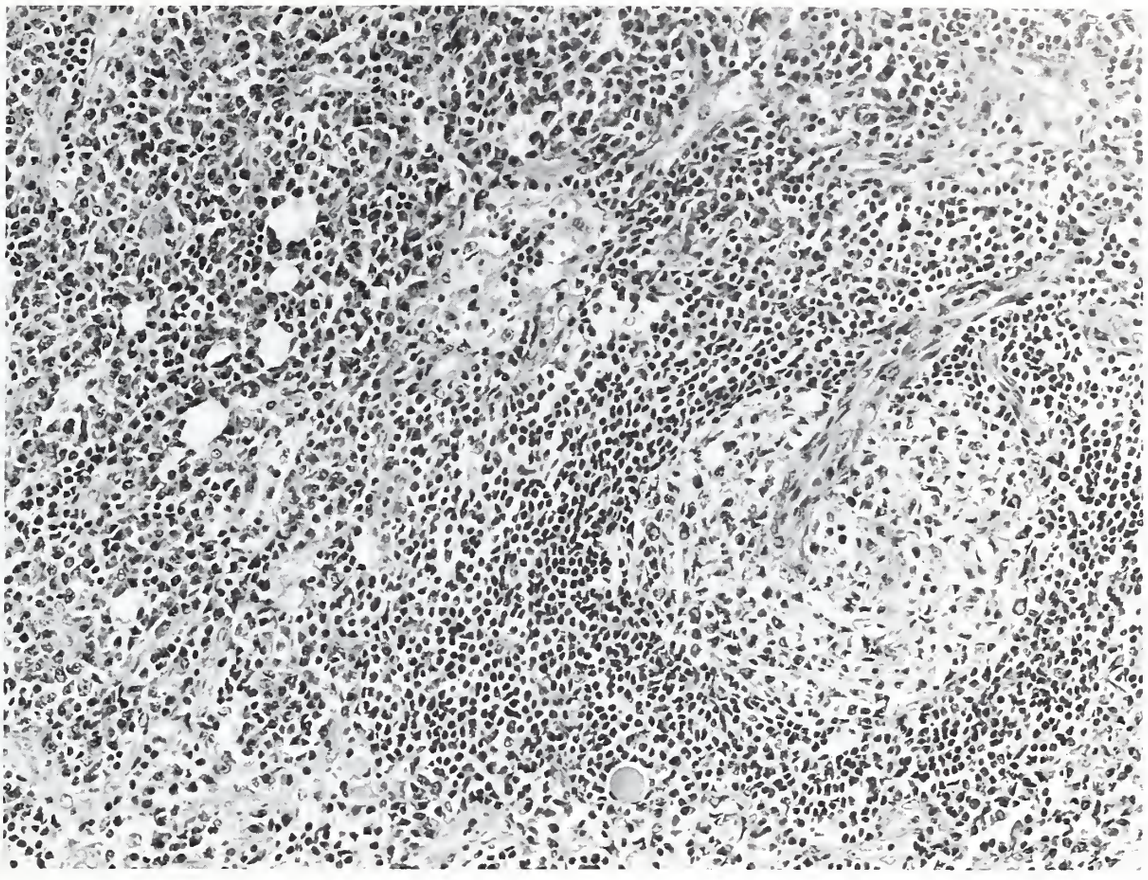


Figure 4-28
CASTLEMAN'S DISEASE, PLASMA CELL TYPE
The interfollicular tissue is crowded with mature plasma cells. Prominent vascularization is also seen. A follicle with a germinal center is seen on the right side. (Figures 4-28 and 4-29 are from the same case.)

The hyaline-vascular type of germinal center is not specific for Castleman's disease. It is occasionally seen as a single follicle in nonspecific reactive lymph nodes, and it has also been reported in lymph nodes of patients with acquired immunodeficiency syndrome (AIDS) and AIDS-related complexes and in patients with angioimmunoblastic lymphadenopathy (44).

Plasma Cell Type. The lesions of the plasma cell type of Castleman's disease range from 3 to 15 cm in diameter and are composed of several discrete, matted nodes or a mass with adjacent smaller nodes. Patients may have constitutional symptoms and signs (44), including anemia, polyclonal gammopathy, elevated erythrocyte sedimentation rate (ESR), bone marrow plasmacytosis, and thrombocytosis. Following complete excision of the mass, the symptoms disappear and laboratory data return to normal. The plasma cell type lesion is most commonly found in the abdomen, usually in the mesentery of the small intestine; fewer are located in the mediastinum and yet fewer in the peripheral nodes. Histologically, the nodal architecture is relatively well preserved. Interfollicular areas are densely infiltrated by plasma cells, sometimes accompanied by numerous Russell bodies (figs. 4-28, 4-29). The germinal centers are numerous but the hyaline-vascular changes are inconspicuous or absent. The overall appearance is reminiscent of that seen in the lymph nodes of patients with rheumatoid arthritis.

Immunohistochemically, the peripheral areas of the abnormal follicles are composed of small lymphocytes expressing the phenotype of mantle zone lymphocytes, and usually, CD5 (38). The central regions of the follicles show abundance of dendritic reticulum cells. Plasma cells produce polyclonal immunoglobulin but several reports have documented a monoclonal plasma cell component, either diffusely replacing the interfollicular area or forming a recognizable nodule (38).

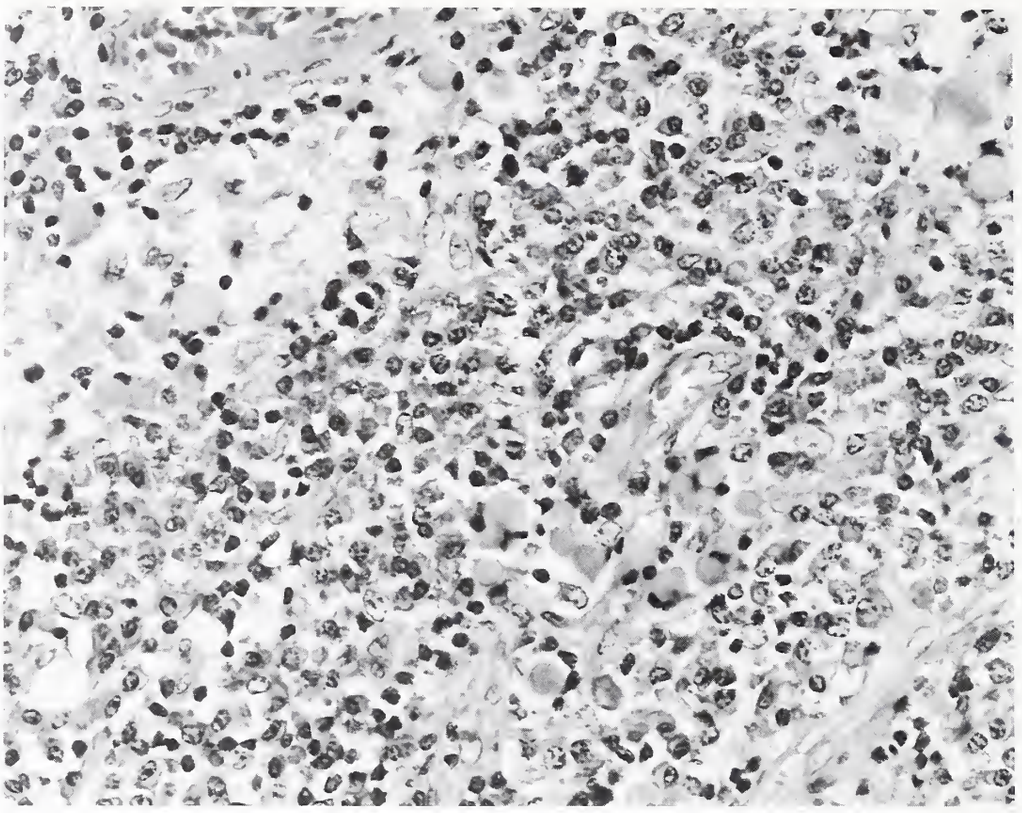


Figure 4-29
CASTLEMAN'S DISEASE, PLASMA CELL TYPE
Higher power magnification of the interfollicular tissue shows the cytologic appearance of the plasma cells, many of which contain Russell bodies.

Castleman's disease has been considered to be a hamartoma or neoplasm, but it is now regarded as a peculiar hyperplastic lymphoid process. Since small lymphocytes surrounding abnormal germinal centers often express CD5, it is postulated that Castleman's disease is a lymphoproliferation of CD5-positive lymphocytes, stimulated by specific lymphokines (38).

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Index*

Acquired immunodeficiency syndrome (AIDS), **25**, 26, **27,** 271
Adenosine deaminase deficiencies, **24**, **25**
Anatomy, mediastinum, 1, **1**
  type of lesions in each anatomic compartment 1, **1**
Aplastic anemia, 108, 110
Autoimmune-related diseases, 108

Biphasic tumor with features of synovial sarcoma, 253, **255**

Carcinoid tumors, thymic
  atypical, 159, **160**, 161
  cellular and structural atypia, **160, 167**, **170**, **180**
  clinical findings, 160, **162**
  combined with thymoma, 181, **181**, **182**
  Cushing's syndrome, 160, 173, **174**, **177**
  definition, 159, **160**
  detection by imaging, 161, **162**
  differential diagnosis, 178
  electron microscopic findings, 169, **174**
  gross findings, 161, **163**
  glandular structure, 168, **171**, **173**
  histogenesis, 159
  immunohistochemical findings, 169, **175, 176, 179, 180**
  incidence, 160
  lipofuscin-like pigment, 163, **168**
  metastasis, 161, 181
  microscopic findings, 161, **164–173**
  mucinous stroma, 168, **172**
  multiple endocrine neoplasia, 160
  producing human chorionic gonadotropin and parathyroid hormone, 176, **178**, **179**
  prognosis, 181
  spindle cell, 159, 168, **172**
  subtyping, 159
  sustentacular cells, 168, **169**, **179**
  treatment, 181
Carcinoma
  distinction between thymic and pulmonary carcinoma, 228
  originating in epithelial inclusion in lymph node or mediastinal soft tissue, 228, **229**
  secondary in mediastinum, 227, **228**
  showing thymus-like differentiation (CASTLE), 38
Carcinoma, thymic
  clinical features, 121, **123**
  combined with thymoma, **126**, 131, **133**, **135**
  definition, 120
  degree of differentiation, 154
  diagnosis (needle biopsy and aspiration cytology), 122, **124**
  differential diagnosis, 155
  Epstein-Barr virus association, 156, **157**
  gross findings, 122, **123, 126**, **127**
  histologic grading (low and high grade), 122, **127**, 154
  imaging (roentgenogram, CT), 122, **123**
  immunohistochemical findings, 128, 151, **152**, 154
    lymphoid cell phenotype, 128, **131**
  incidence, **42**, 121
  metastasis, 122, **125**
  microscopic findings and histologic subtypes, 124, **127–130, 132, 133, 135–140, 142–147, 149–152**
  morphology and functional correlations, 155
  perivascular space, probable, 128, **130**, **132**
  prognostic and malignancy-associated factors, 153, **153**
  TNM classification and staging, **118**, 122, **125**, 153, **153**
  treatment, 122
Carcinoma, thymic, types
  adenocarcinoma, 136, **142**, **143**
  adenosquamous, 35, 134, **140, 141**
  basaloid, **127**, 134, **136**, **137**
  clear cell, 150, **150**
  combined small cell and adenocarcinoma, 148, **149**
  combined small cell and large cell, 148, **150**
  large cell, 141, **145**, **146**
  large cell neuroendocrine, 159, **160,** 178
  lymphoepithelioma-like, 138, **144**
  mucoepidermoid, 134, **138, 139**
  sarcomatoid, 151, **151**, **152**
  small cell/neuroendocrine, 141, **148**, 159, **160**
  squamous cell, 127, **128–133**, **135**
  well-differentiated thymic carcinoma, 152, 155, *also see* Thymoma
Castleman's disease, 267, **267–272**
  hyaline vascular type, 268, **268–270**
  plasma cell type, 271, **271**, **272**
Choriocarcinoma, **192**, 201, **204–206**
Classification, thymic tumors, 33, **34**, **35**, **88**
  controversies, 87, **88**
Cyst
  acquired thymic multilocular, 233, 236, **236**, **237**
  congenital, 233, **263**
    bronchogenic, 264, **264, 265**
    celomic (pericardial and mesothelial), 266, **266**
    esophageal, 265
    gastroenteric, 265
    thoracic duct, 266
    thymic, 233, **233–235**

DiGeorge's syndrome, 25
Down's syndrome, 25, **26**

Ectopic tissue, anterosuperior mediastinum, 237
  adenomatous goiter, 237, **237**, **238**
  parathyroid gland, 238, **239**
Ectopic tumors, 237
  hamartomatous thymoma, *see* Lesion, hamartomatous
  parathyroid adenoma, 238, **239**
  thyroid adenoma, 237
Embryonal carcinoma, 198
Ependymoma, mediastinal, 261
Epithelioid hemangioendothelioma, 256

Fibromatosis, 251, **253**

*Numbers in boldface indicate table and figure pages.

Fibrous mediastinitis, 251, **252**

Ganglioneuroblastoma, 260, **261**
Ganglioneuroma, 258, **259**
Germ cell tumors
  alpha-1 fetoprotein (AFP), 185, 200
  biopsy, 185, **190–192**
  choriocarcinoma, *see* Choriocarcinoma
  classification, 183, **183**
  clinical findings, 184
  definition, 183
  diagnosis, 185, **186–192**
  embryonal carcinoma, *see* Embryonal carcinoma
  germinoma (seminoma dysgerminoma), *see* Germinoma
  gross findings, 185, **185**, **189**, **193**, **194**
  hematologic malignancies, 185
  human chorionic gonadotropin (hCG), 185, **201**, **206**
  incidence, **42,** 184, **184**
  Klinefelter's syndrome, 184, 200
  microscopic findings, 186, **193**, **195–197**
  placental alkaline phosphatase, 198, 200, **200**, 201
  prognosis, 203
  roentgenologic findings, 185, **186–189**
  teratoma, *see* Teratoma
  treatment, 203, **204–206, 208, 209**
  yolk sac tumor (endodermal sinus tumor), *see* Yolk sac tumor
Germinoma (seminoma, dysgerminoma), **186**, **187**, **190**, 198, **200**
Graft versus host disease (GVHD), **25**, 26

Hamartomatous lesions, 33
  ectopic hamartomatous thymoma, 38, **39**, **40**
Hassall corpuscles, *see* Thymus gland
Hemangioma, 250, **251**
Hodgkin's disease, *see* Malignant lymphoma
Hypogammaglobulinemia, 43, 108, 110

Immunodeficiency, *see* Thymus gland
Interdigitating reticulum cells, 14, **17, 103**

Klinefelter's syndrome, *see* Germ cell tumors

Lesion
  atypical lymphoepithelial, *see* Thymus gland
  cyst-like, **263,** 266
  hamartomatous, 33
  tumor-like, 236
Liposarcoma, 253, **254**
Lymph follicles, 14, **16**, **30**, **31**, 109, **109**
Lymphangioma, 249, **250**
Lymphocytes (thymocytes), 11
  immature (cortical) T lymphocytes, **18**, 45, 100, **102**, **106**
  maturation 17, **18**
Lymphoma, malignant, *see* Malignant lymphoma

Macrophages, 14, **16**
Major histocompatibility complex (MHC) antigen deficiency, 25, **25**
  in thymic epithelial tumors, 99, **101**, 154
Malignant lymphoma, 207
  clear cell lymphoma (B-cell type), 221
  Hodgkin's disease, 207, **209–212**
  large cell anaplastic lymphoma, 214
  large cell lymphoma with sclerosis, 214, 215, **216–220**
  lymphoblastic lymphoma, 212, **213–215**
  mucosa-associated lymphoid tissue (MALT) lymphoma, 221, **222–227**
  pleomorphic large cell lymphoma, 215
Malignant peripheral nerve sheath tumor, 258
Mediastinal goiter and adenoma, *see* Ectopic tissues and tumors
Mediastinal parathyroid gland and adenoma, *see* Ectopic tissues and tumors
Mesenchymal tumors
  benign, 249, **249–253**
  malignant, 253, **254**, **255**
Mesothelioma, 229
  benign localized fibrous mesothelioma, *see* Tumor, solitary fibrous
  malignant desmoplastic mesothelioma, 231
Myasthenia gravis, 28, **31**, 38, 42, *also see* Thymoma
  pathogenesis (antiacetylcholine receptor and antititin), 109
Myoid cells, 2, 17, **17**, **103**, *also see* Thymoma

Neuroblastoma, 259, **260**, **261**, 263
Neurofibroma, 256, **258**
Neurofibromatosis, 258
Neurofibrosarcoma, *see* Malignant peripheral nerve sheath tumor
Neurogenic tumors, 256, **256–262**, 263

Paragangliomas, 262, **262**
Parathyroid gland, 3, *also see* Ectopic tissues
Peripheral nerve sheath tumor, malignant, 258
Pigmented neuroectodermal tumor (melanotic progonoma, retinal anlage tumor), 262
Primitive neuroectodermal tumor (PNET), 261
Pure red cell aplasia, see Thymoma

Rhabdomyosarcoma, 253

Schwannoma (neurilemmoma, neurinoma), 256, **256**, **257**
Solitary fibrous tumor, 229, **230–232**
  immunohistochemistry, 229, **231**
  malignant, 229, **232**
  with hypoglycemia, 229
Spindle epithelial tumor with thymus-like differentiation (CASTLE), 38
Systemic lupus erythematosus, 43, 108

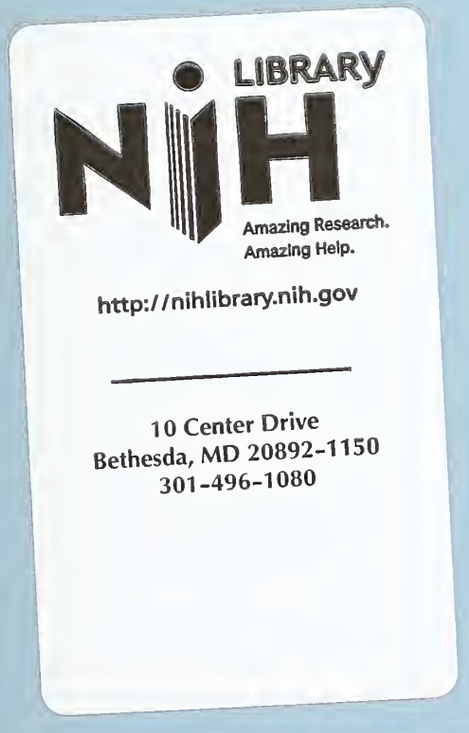
Teratoma (mature and immature), **183,** 185, **185, 193 195–197**, **199**, **200**
  malignant with germ cell tumor, **183**
  malignant with non-germ cell tumor, **183**, **199**, 201, **207**
Thymic carcinoma, *see* Carcinoma, thymic
Thymic cyst, *see* Cyst, thymic
Thymocytes, *see* Lymphocytes
Thymolipoma, 33
  gross features, 33, **36**, **37**
  microscopic features, 33, **36**, **37**
  imaging (X-ray, CT, ultrasonography) diagnosis, 36

Thymoma
B lymphocytes, 101
calcification, **45**, 56
classification, **35**, 41, 87, **88**
clear cell change, 88, **92**
clinical findings, 42
clinical staging, 117, **118–120**
Masaoka's clinical stage, **118**
modified, **75**, **119**
Yamakawa-Masaoka TNM classification and staging, **118**
combined with carcinoid tumor, 181, **181**. **182**
complications, 42
conditions and diseases associated, 107
cortical type epithelial cells, **69–71**, 73
cystic changes, **52**, 54, **55**, **56**
definition, 41
diagnosis, 43, **44–53**
biopsy, 43, **48**, **49**, **53**
cytologic, 43, **50–52**
histologic, 43, **48**, **49**
imaging, 43, **44–47**
differential diagnosis, 95
ectopic (cervical and pulmonary), 38, 42, **43**
epithelial cell atypia, **71**, **74**
function, 41, 97, 101
glandular structures, **84**, **86**, 92
gross findings, 45, **45**, **54–57**
Hassall corpuscles, **79**, 88, **89**, **90**
hemangiopericytomatous features, **82**, 92
histologic classification, **34**, **35**
implantation, 45, **46**, **57**, **62**
immunohistochemistry, 45, 97, **98–103**
incidence, 41, **42**
interdigitating reticulum cells, 101, **103**
lymph follicles, 109, **109**
lymphocytes (thymocytes), *see* Lymphocytes
medullary differentiation, **48**, 77, **78**, **79**, **102**, **103**
medullary type epithelial cells, **72**, 73, **73**
melanocytes, 93, **95**, **98**
metastasis, 45
microscopic findings, 56
mucus-producing cells, **86**
multiple thymomas, 56
myasthenia gravis, 99, 107, **111**, 117, 156
myoid cells, 93, **93**, **94**, **103**
nuclear area, 113, **115**
nuclear DNA content, 113, **116**
ossification, 56, **58**
papillary pattern, **85,** 92
paraneoplastic syndrome and associated disease, 107
perivascular spaces, 59, **66–68**, **107**
prognostic factors, **75**, 110, **111, 112, 119**
progression to thymic carcinoma, 131, **133**, **135**
proliferative activity, 116
pure red cell aplasia, 108, 110
recurrence, 117
squamous differentiation, 88, **90**
squamous metaplasia, 88, **89**
subtypes, 56
T-cell maturation, 41
TNM classification and staging, 117, **118**, **120**
treatment, 117
type I malignant thymoma, *see* invasive thymoma in Thymoma, types
type II malignant thymoma (carcinoma, thymic), **35**, 120
ultrastructural findings, 101, **104–108**
well-differentiated thymic carcinoma versus thymoma, **68**, **71**, **81**, 83, 87, 101, 155
Thymoma, ectopic hamartomatous, 38, **39**. **40**
Thymoma, types
atypical, 41, **71**, **74**, **81**, 87
biphasic (polygonal and spindle cells), 93, **96**
circumscribed, **35**, 45, **45**, **55**
clear cell type, 88, **91**
cortical, **70**, **71**, 83
encapsulated, **35**, 45, **54–56**, **58**
epithelial cell predominant, **49**, 69
invasive, **35**, 45, **46**, **53**, **56**, **57**, **62–64**
lymphocyte predominant, **48**, 69, **76–79**, **98**
medullary, **72**, **73**, 80, **82–86**, **99**, **100**, **113**, **114**
microscopic, 45, **59–61**
mixed lymphocytic and epithelial, **50**, **65**, 69, **69**, **71**, **89**
mixed medullary and cortical, **65**, 80, **80**, **96**, **98**
mixed polygonal and spindle cell, **51**, **65**
noninvasive, **35**, **44**, 45
plasma cell rich, 95
polygonal cell type with epidermoid arrangement, **68**, **71**, 79, **81**
polygonal (oval) cell type, 35, **50**, 69, **69–71**
predominantly cortical, **78**, **79**, 83
rhabdomyomatous, 93, **94**
rosette-forming type, **82**, **83**, 88, **113**
spindle cell type, **35**, **49, 52, 72, 73,** 110, **114**
Thymus gland
atrophy, 23, **23**, **25**, **27**
atypical lymphoepithelial lesion, 221
dysplasia, 23, **23–26**
adenosine deaminase deficiency, 24
DiGeorge's syndrome, 25
Down's syndrome, 25, **26**
severe combined immunodeficiency (SCID), **24**, **25**
ectopic thymus, 2, **3**
embryology, 1, **2**
epithelial cells, 6, **6–13**
cortical, 6, **6**, **7**
medullary, 6, **6**, **7**
gross findings, 4, **4**
Hassall corpuscles, 8, **14**, **15**
hyperplasia
lymphoid, 28, **29–31**
true, 27, **28**, **29**
with features of Castleman's disease, 29, **31**
immunodeficiency, 23
primary (inherited), 23, 23–26
secondary (acquired), 23, **23**, **25**, **27**
immunohistochemistry, 7, **12–14**
involution, 18, **19–22**
Langerhans cells, 14
location, 3, **3**
lymphocytes (thymocytes), *see* Lymphocytes
maturation of thymocytes, 17, **18**
microscopic features, 5, **6, 7**
myoid cells, 17

non-neoplastic conditions, 23
normal thymus, 1
thymic hormones, 8, 11
tumor classification, 33, **34**, **35**
ultrastructure, 6, **9–11**
weight, **5**, 27, **28**
Tumor-like lesions, thymus, 233
Tumors
biphasic, with features of synovial sarcoma, 253, **255**
carcinoid, *see* Carcinoid tumor
ectopic, *see* Ectopic tumors
germ cell, *see* Germ cell tumors
mesenchymal, *see* Mesenchymal tumors
neurogenic, *see* Neurogenic tumors
solitary fibrous, *see* Solitary fibrous tumor
thymic, 33
classification, 33, **34**, **35**
epithelial cell, 40, *also see* Thymoma and Carcinoma, thymic

Well-differentiated (organotypical) thymic carcinoma, *see* Thymoma and Thymoma, types, atypical

Yolk sac tumor (endodermal sinus tumor), **191**, 201, **202**, **203**, **208**, **209**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